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(54) **Hydroxydiphenyl ether compounds**

(57) The present invention relates to the use of hydroxydiphenyl ether compounds as antimicrobially ac-

tive substances, to certain new compounds of this type and to processes for the preparation of these compounds.

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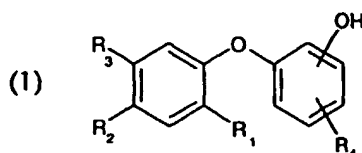
Description

[0001] The present invention relates to the use of hydroxydiphenyl ether compounds as antimicrobially active substances, to certain new compounds of this type and to processes for the preparation of these compounds.

[0002] It is known that certain halogenated diphenyl ether compounds have an excellent antimicrobial activity. These compounds are therefore widely used, for example as active substances for the antimicrobial finishing of medical items and household articles, as detergent additive and in the hygiene sector, for example in soaps or dental hygiene products. Such halogenated compounds are described in DE 2538016. However it is desirable to be able to provide non-halogenated agents which are highly effective antimicrobial agents. Polymeric materials can be antimicrobially finished by incorporating halogenated diphenyl ether compounds, the active substances being, as a result of their excellent migration properties, constantly conveyed to the surface of the corresponding material ("slow release"). For certain industrial applications, this effect is undesired since the long-term effect of antimicrobially finished materials such as textiles, paper, plastics, cellulose sponges etc. is reduced at the same time.

[0003] The object of the present invention is thus to provide non-halogenated hydroxydiphenyl ether compounds for use as antimicrobially active substances and which, at the same time, are stable to migration.

[0004] The present invention provides the use of hydroxydiphenyl ether compounds of the following formula



wherein when OH is in the para position with respect to the ether linkage

R₁ and R₂ are independently of each other hydrogen, hydroxy, C₁-C₂₀alkyl, C₅-C₇cycloalkyl, C₁-C₆alkylcarbonyl, C₁-C₂₀alkoxy, phenyl or phenyl-C₁-C₃alkyl;

R₃ is hydrogen, C₁-C₂₀alkyl or C₁-C₂₀alkoxy;

R₄ is hydrogen, C₁-C₂₀alkyl, hydroxy substituted C₁-C₂₀alkyl, C₅-C₇cycloalkyl, hydroxy, formyl, acetonyl, C₁-C₆alkylcarbonyl, C₂-C₂₀alkenyl, carboxy, carboxyC₁-C₃alkyl, C₁-C₃alkylcarbonylC₁-C₃alkyl or carboxyallyl;

wherein when OH is in the meta position with respect to the ether linkage

R₂ is hydrogen, C₁-C₂₀alkyl, hydroxy substituted C₁-C₂₀alkyl or C₁-C₆alkylcarbonyl;

R₁ and R₃ are independently of each other hydrogen, C₁-C₆alkylcarbonyl or C₁-C₂₀alkyl;

R₄ is hydrogen, C₁-C₂₀alkyl, hydroxy substituted C₁-C₂₀alkyl, C₅-C₇cycloalkyl, hydroxy, formyl, acetonyl, C₁-C₆alkylcarbonyl, C₂-C₂₀alkenyl, carboxy, carboxyC₁-C₃alkyl, C₁-C₃alkylcarbonylC₁-C₃alkyl or carboxyallyl;

wherein when OH is in the ortho position with respect to the ether linkage

R₁ is hydrogen, C₁-C₆alkyl carbonyl or C₁-C₂₀alkyl;

R₄ is hydrogen, C₁-C₂₀alkyl, hydroxy substituted C₁-C₂₀alkyl, C₅-C₇cycloalkyl, hydroxy, formyl, acetonyl, C₁-C₆alkylcarbonyl, C₂-C₂₀alkenyl, carboxy, carboxyC₁-C₃alkyl, C₁-C₃alkylcarbonylC₁-C₃alkyl or carboxyallyl;

R₂ and R₃ are independently of each other hydrogen, C₁-C₆alkyl carbonyl or C₁-C₂₀alkyl;

with the proviso that compounds wherein OH is in the para position with respect to the ether linkage and R₁ and R₃ are both hydrogen and R₂ is methoxy or methyl; or a compound wherein OH is in the para position with respect to the ether linkage R₂ is hydrogen, R₁ is isopropyl and R₃ is methyl are excluded; as antimicrobial agents.

[0005] C₁-C₂₀alkyl is straight-chain or branched alkyl radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, tert-pentyl, hexyl, cyclohexyl, heptyl, octyl, isooctyl, nonyl or decyl and the like.

[0006] C₁-C₂₀alkoxy is straight-chain or branched alkoxy radicals such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentyloxy, iso-pentyloxy, tert-pentyloxy, heptyloxy, octyloxy, isooctyloxy, nonyloxy or decyloxy and the like.

[0007] C₁-C₆alkyl carbonyl is straight-chain or branched carbonyl radicals such as acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl or pivaloyl and the like.

[0008] Hydroxy substituted C₁-C₂₀alkyl is hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, hydroxyheptyl, hydroxyoctyl, hydroxynonyl or hydroxydecyl and the like.

[0009] Preferably compounds of formula (1) are used wherein, when OH is in the para position with respect to the ether linkage

R₁ and R₂ are independently of each other hydrogen, C₁-C₂₀alkyl, C₁-C₆ alkyl carbonyl or C₁-C₂₀alkoxy;

R₃ is hydrogen, C₁-C₂₀alkyl or C₁-C₂₀alkoxy;

R₄ is hydrogen, C₁-C₂₀alkyl, hydroxy, formyl, acetonyl, allyl, carboxymethyl, carboxyallyl, hydroxy substituted C₁-C₂₀alkyl or C₁-C₆ alkyl carbonyl;

wherein when OH is in the meta position with respect to the ether linkage

R₂ is hydrogen, C₁-C₂₀alkyl, hydroxy substituted C₁-C₂₀alkyl or C₁-C₆alkyl carbonyl;

R₁ and R₃ are independently of each other hydrogen, C₁-C₆alkyl carbonyl or C₁-C₂₀alkyl;

R₄ is hydrogen, C₁-C₂₀alkyl, hydroxy, formyl, acetonyl, allyl, carboxymethyl, carboxyallyl, hydroxy substituted C₁-C₂₀alkyl or C₁-C₆ alkyl carbonyl;

wherein when OH is in the ortho position with respect to the ether linkage

R₁ is hydrogen, C₁-C₆ alkyl carbonyl or C₁-C₂₀alkyl;

R₄ is hydrogen, C₁-C₂₀alkyl, hydroxy, formyl, acetonyl, allyl, carboxymethyl, carboxyallyl, hydroxy substituted C₁-C₂₀alkyl or C₁-C₆ alkyl carbonyl;

R₂ and R₃ are independently of each other hydrogen, C₁-C₆ alkyl carbonyl or C₁-C₂₀alkyl;

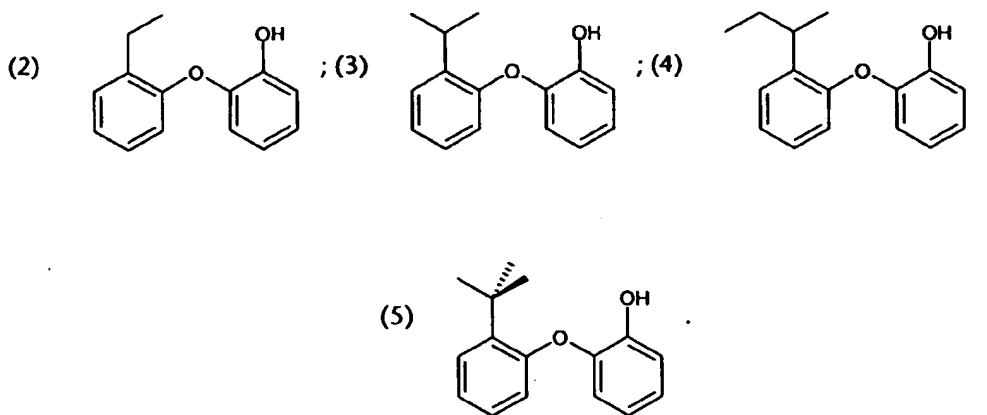
with the proviso that compounds wherein OH is in the para position with respect to the ether linkage and R₁ and R₃ are both hydrogen and R₂ is methoxy or methyl; or a compound wherein OH is in the para position with respect to the ether linkage R₂ is hydrogen, R₁ is isopropyl and R₃ is methyl are excluded.

[0010] Another aspect of the invention are certain compounds described by formula (1) which are novel.

[0011] These novel compounds are of formula (1) wherein when OH is in the ortho position with respect to the ether linkage and R₂, R₃ and R₄ are hydrogen and R₁ is C₁-C₂₀alkyl.

[0012] Preferably these novel compounds are of formula (1) wherein when OH is in the ortho position with respect to the ether linkage and R₂, R₃ and R₄ are hydrogen and R₁ is C₁-C₅alkyl.

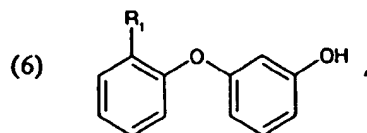
[0013] Compounds of particular interest include the following:



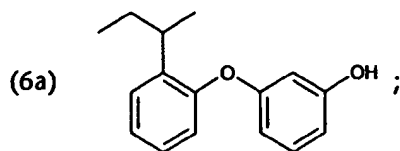
[0014] Further novel compounds are of formula (1) wherein when OH is in the meta position with respect to the ether linkage and R₂, R₃ and R₄ are hydrogen and R₁ is C₁-C₂₀alkyl.

[0015] Preferably these novel compounds are of formula (1) wherein when OH is in the meta position with respect to the ether linkage and R₂, R₃ and R₄ are hydrogen and R₁ is C₁-C₅ alkyl.

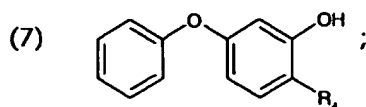
[0016] Compounds of particular interest include the following:



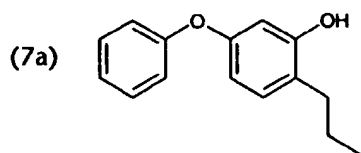
wherein R₁ is C₁-C₅alkyl; for example the compound of formula



or compounds of formula



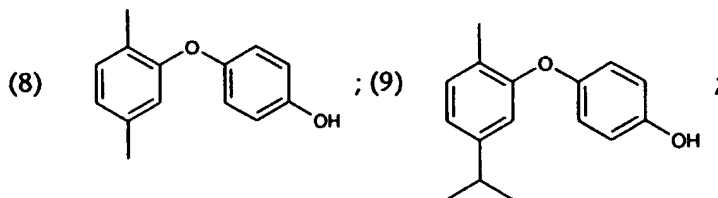
wherein R₄ is C₁-C₅alkyl, for example the compound of formula

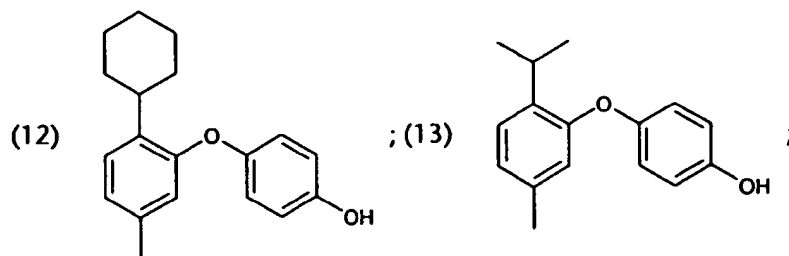
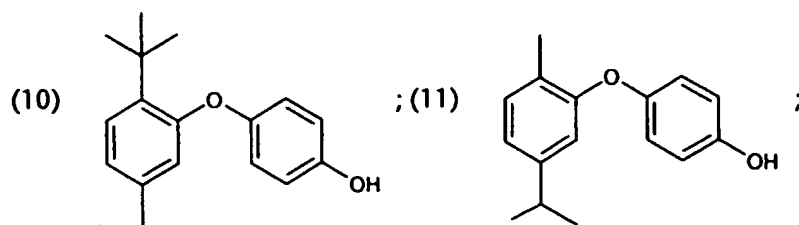


[0017] Further novel compounds are of formula (1) wherein when OH is in the para position with respect to the ether linkage and R₂ and R₄ are hydrogen and R₁ and R₃ are C₁-C₂₀alkyl.

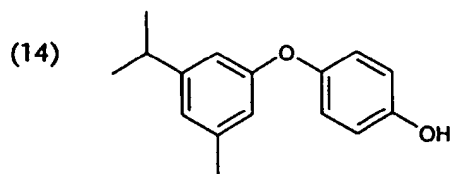
[0018] Preferably these novel compounds are of formula (1) wherein when OH is in the meta position with respect to the ether linkage and R₂ and R₄ are hydrogen and R₁ and R₃ are C₁-C₅ alkyl.

[0019] Compounds of particular interest include the following:



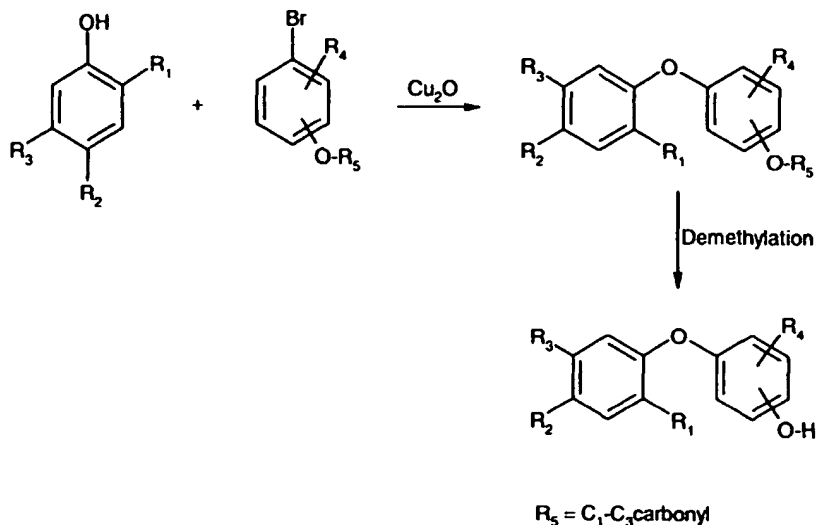


or



[0020] Another aspect of the present invention is a process for the preparation of compounds of formula (1) wherein when OH is in the ortho position with respect to the ether linkage and R_2 , R_3 and R_4 are hydrogen and R_1 is C_1 - C_{20} alkyl, compounds of formula (1) wherein when OH is in the meta position with respect to the ether linkage and R_2 , R_3 and R_4 are hydrogen and R_1 is C_1 - C_{20} alkyl and compounds of formula (1) wherein when OH is in the para position with respect to the ether linkage and R_2 and R_4 are hydrogen and R_1 and R_3 are C_1 - C_{20} alkyl.

[0021] The process comprises reacting a substituted phenol with an ether substituted halogenphenol in the presence of alkali and a catalytically active quantity of copper or of a copper compound, and the resulting alkyloxybenzol compound is then heated in the presence of hydrogen halide and acid in order to convert the alkyloxy group to a hydroxy group. An example of the reaction scheme is shown below, wherein R represents one of the groups R_1 , R_2 or R_3 .



[0022] Preferred combinations of reagents include 2- C_1 - C_{20} alkyl substituted phenols and 2-methoxy-bromophenol.

[0023] Other preferred combinations of reagents include 2- C_1 - C_{20} alkyl substituted phenols and 3-methoxy-bromophenol.

[0024] Other preferred combinations of reagents include 2,5- C_1 - C_{20} dialkyl substituted phenols and 4-methoxy-bromophenol. Preferred bases are hydroxides/carbonates from group 1/2 metals.

[0025] The alkali required for the reaction can be added in different forms. For example the substituted phenol can be reacted in the form of alkali phenolate. It is also possible to introduce for example solid potassium hydrate into the mixture of phenol and halogenphenol, in which case homogeneity can be achieved by heating to 120 to 130°C. It is also possible to use aqueous alkali solutions and remove the water during the reaction, for example by azeotropic distillation in the presence of an organic entraining agent.

[0026] The reaction may be also carried out in the presence of a solvent such as an aliphatic ether containing 6 or more carbon atoms and boiling at a temperature above 130°C and also ethers of polyglycols such as di- and tri-ethylene glycol and in high boiling solvents as Pyridin, DMF, DMA, DMSO, Toluene, Xylene etc.

[0027] General catalysts for Ullmann condensation are Cu, Cu_2Cl_2 , bas. $CuCO_3$, $CuCl_2$, CuO or Cu_2O . Copper or copper compounds are used in known manner as catalysts for example in quantities of from 0.1 to 2.5% based on the halogenphenol. The reaction temperatures are generally from 150°C to 200°C whilst the reaction times vary from 1 to 16 hours. The reaction may be carried out under elevated pressure.

Suitable reagents used in the demethylation step include hydrogen bromide. Suitable acids used in the demethylation step include acetic acid. General reagents are $AlCl_3$, BCl_3 , BF_3 , HBr, HI, preferably pyridinium x HCl.

[0028] The reaction can be worked up in the usual way. Unreacted starting materials can be separated off by distillation, optionally under vacuum.

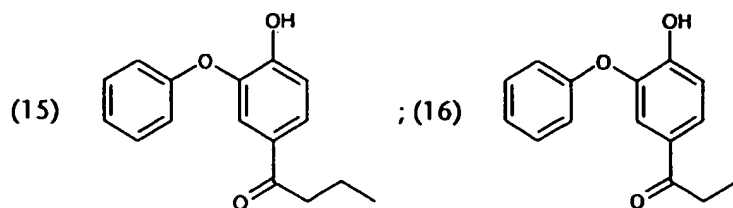
[0029] A further aspect of the invention includes other certain compounds described by formula (1) which are novel.

[0030] These novel compounds are of formula (1) wherein when OH is in the ortho position with respect to the ether linkage

R_1 , R_2 and R_3 are hydrogen;

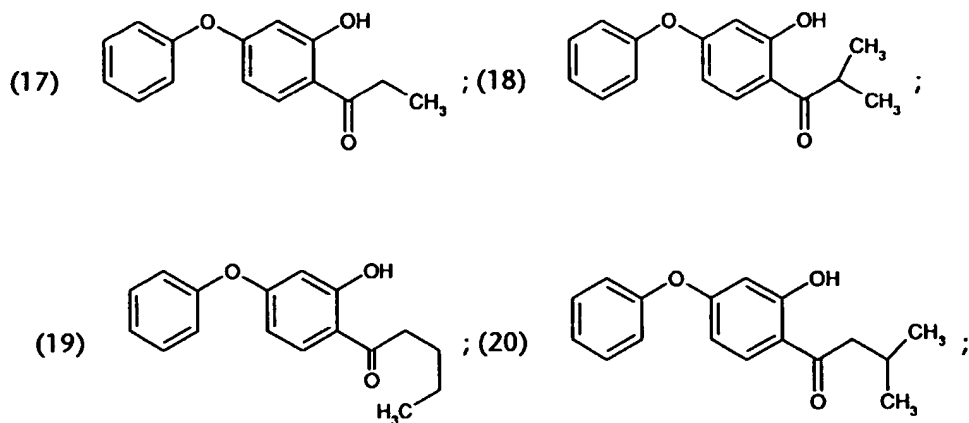
R_4 is in the meta position with respect to the ether linkage and is C_1 - C_6 alkyl carbonyl.

[0031] Compounds of particular interest include the following:

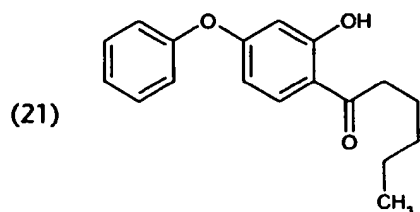


further novel compounds are of formula (1) wherein when OH is in the meta position with respect to the ether linkage and R_1 , R_2 and R_3 are hydrogen and R_4 is in the para position with respect to the ether linkage and is C_1 - C_6 alkyl carbonyl.

[0032] Compounds of particular interest include the following:

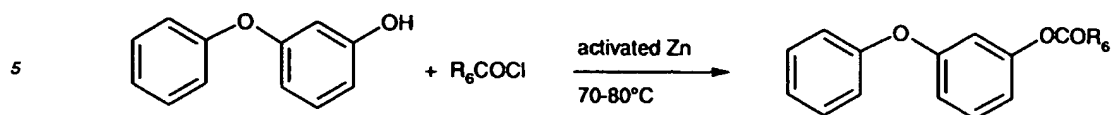


or

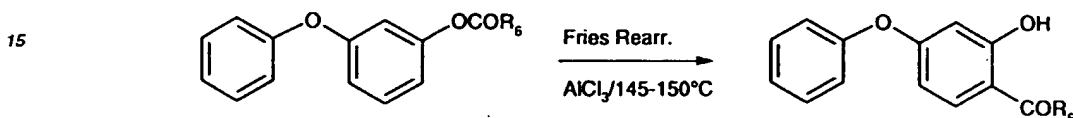


[0033] A further aspect of the present invention is another process for the preparation of compounds of formula (1) wherein when OH is in the meta position with respect to the ether linkage and R_1 , R_2 and R_3 are hydrogen and R_4 is in the para position with respect to the ether linkage and is C_1 - C_6 alkyl carbonyl and also for compounds of formula (1) wherein when OH is in the ortho position with respect to the ether linkage and R_1 , R_2 and R_3 are hydrogen and R_4 is in the meta position with respect to the ether linkage and is C_1 - C_6 alkyl carbonyl.

[0034] The process comprises reacting an acyl chloride with a phenoxyphenol, such as meta-phenoxyphenol or ortho-phenoxyphenol, in the presence of activated zinc at a temperature of between 70°C to 80°C. The hydroxyl group undergoes acylation, as shown in the scheme below:



10 [0035] This acyl compound then undergoes a "Fries rearrangement" in the presence of aluminium chloride at a temperature of $145^\circ C$ to $150^\circ C$, producing an acylated phenol.



20 [0036] Preferably R_6 is C_1-C_6 alkylcarbonyl.

[0037] These compounds may also be amenable by direct acylation of phenols with catalysts such as Lewis acids as $AlCl_3$, $ZnCl_2$, $FeCl_3$, BCl_3 , BF_3 , transition metal trifluorosulfonates (eg. $Sc(OTf)_3$) in inert solvents as EDC, CH_2Cl_2 , CS_2 or nitrobenzene.

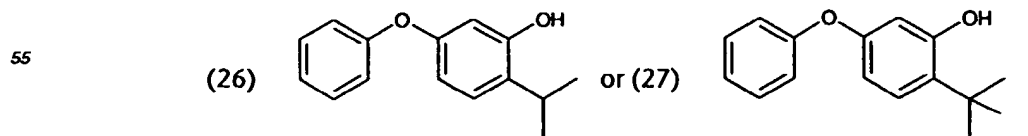
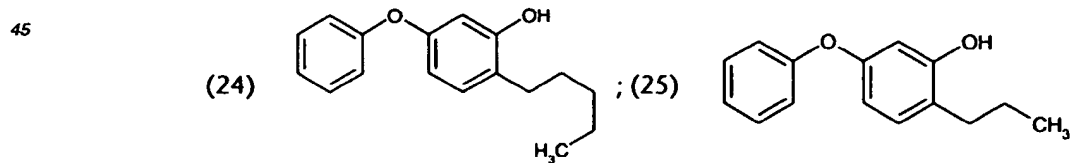
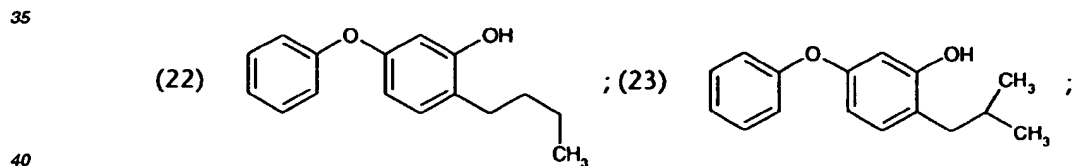
25 [0038] Further novel compounds are of formula (1) wherein when OH is in the meta position with respect to the ether linkage and R_1 , R_2 and R_3 are hydrogen and R_4 is in the para position with respect to the ether linkage and is C_1-C_{20} alkyl.

[0039] Preferably these novel compounds are of formula (1) wherein when OH is in the meta position with respect to the ether linkage

30 R_1 , R_2 and R_3 are hydrogen;

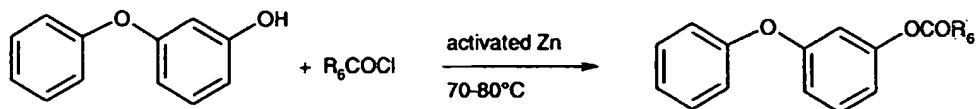
R_4 is in the para position with respect to the ether linkage and is C_1-C_5 alkyl.

[0040] Compounds of particular interest include the following:

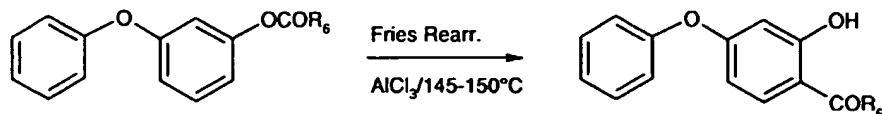


[0041] A further aspect of the present invention is another process for the preparation of compounds of formula (1) wherein when OH is in the meta position with respect to the ether linkage and R_1 , R_2 and R_3 are hydrogen and R_4 is in the para position with respect to the ether linkage and is C_1 - C_{20} alkyl.

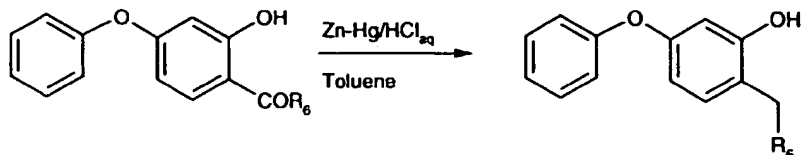
[0042] The process comprises reacting an acyl chloride with meta-phenoxyphenol in the presence of activated zinc at a temperature of between 70°C to 80°C. The hydroxyl group undergoes acylation, as shown in the scheme below:



[0043] This acyl compound then undergoes a "Fries rearrangement" in the presence of aluminium chloride at a temperature of 145°C to 150°C, producing an acylated phenol.



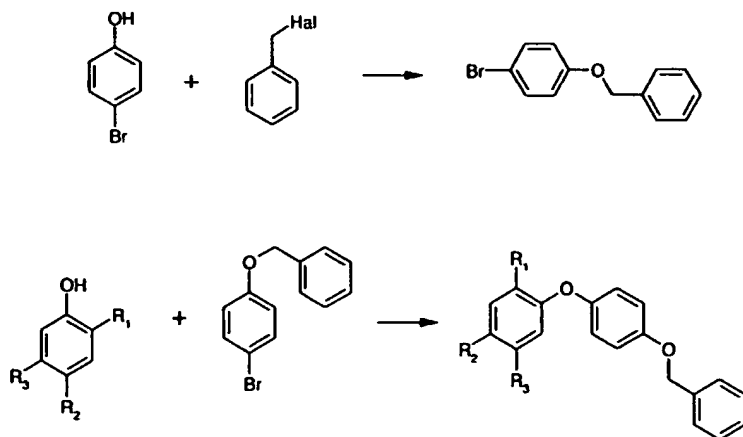
[0044] This acylated phenol is then refluxed in the presence of amalgamated zinc, hydrochloric acid and a solvent such as toluene, to yield the end product.

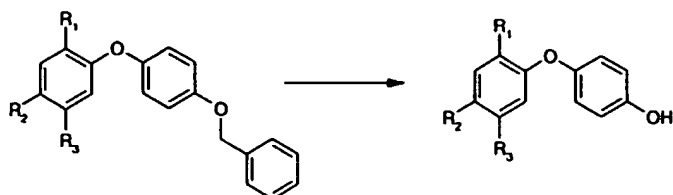


R_6 is C_1 - C_{19} alkyl.

[0045] Reduction to these compounds is also achieved by catalytic hydrogenation.

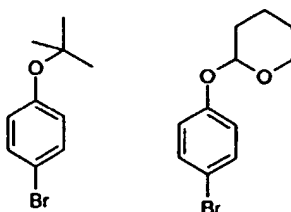
[0046] Alternatively, compounds of formula (1) wherein the hydroxy group is in para position with respect to the ether linkage can be obtained by the "benzylic ether route" according to the following reaction scheme:





[0047] This is basically the same synthesis route as described above but it's applying the benzylic ether of p-bromo phenol instead of the methyl ether.

[0048] The following ether compounds can also be employed:



[0049] The hydroxydiphenyl ether compounds according to the invention are thermally stable and antimicrobially effective compounds of low volatility and having a severely reduced tendency to migrate. They are therefore suitable for the antimicrobial finishing of polymeric compounds, for example in plastics, rubbers, paints, surface coatings, (textile) fibres which are exposed to a microbially contaminated environment.

[0050] Examples of polymers and other substrates which can be antimicrobially finished in this way are:

- polymers of mono- and diolefins,
- polyolefins,
- copolymers of mono- and diolefins with one another or with other vinyl monomers,
- hydrocarbon resins,
- polystyrene,
- copolymers of styrene or α -methylstyrene or dienes or acrylic derivatives,
- graft copolymers of styrene or α -methylstyrene.
- halogen-containing polymers,
- polymers derived from α,β -unsaturated acids and derivatives thereof, such as polyacrylates and polymethacrylates,
- polymers derived from unsaturated alcohols and amines or acyl derivatives or acetals thereof,
- homo- and copolymers of cyclic ethers, polyacetals, polyphenylene oxides and polyphenylene sulfides and mixtures thereof with styrene polymers or polyamides,
- polyurethanes derived from polyethers, polyesters and polybutadienes having terminal hydroxyl groups on the one hand and aliphatic or aromatic polyisocyanates on the other, and precursors thereof,
- polyamides and copolyamides derived from diamines and dicarboxylic acids and/or from aminocarboxylic acids or the corresponding lactams,
- polyureas, polyimides, polyamide-imides, polyetherimides, polyesterimides, polyhydantoins and polybenzimidazoles,
- polyesters,
- polycarbonates and polyester carbonates,
- polysulfones, polyether sulfones and polyether ketones,
- crosslinked polymers derived from aldehydes on the one hand and phenols, urea or melamine on the other hand, such as phenol-formaldehyde resins, urea-formaldehyde resins and melamine-formaldehyde resins,
- drying and non-drying alkyd resins,
- unsaturated polyester resins,
- crosslinkable acrylic resins,
- alkyd resins, polyester resins and acrylate resins,
- crosslinked epoxy resins,

- superabsorbent polymers
- natural polymers, such as cellulose, natural rubber, gelatine, and derivatives thereof modified chemically in a polymer-homologous manner, such as cellulose acetates, cellulose propionates cellulose butyrates, or the cellulose ethers, such as methylcellulose; and also rosins and derivatives.

[0051] The invention thus also provides a composition comprising

- (A) an organic material to be antimicrobially finished and
- (B) a compound of the formula (1).

[0052] The invention also relates to a process for the antimicrobial finishing of an organic material, which comprises adding at least one compound of the formula (1) thereto, and to the use of the compound of the formula (1) for the antimicrobial finishing of polymeric materials.

[0053] The amount of antimicrobial active substance to be used depends on the organic material to be antimicrobially finished and on the intended use of the material finished in this way. The composition according to the invention generally comprises, per 100 parts by weight of component (A), from 0.01 to 15 parts by weight, in particular from 0.05 to 10 parts by weight, and especially from 0.1 to 5 parts by weight of the antimicrobial active substance (component (B)).

[0054] The antimicrobial active substance (component (B)) can also be a mixture of two or more compounds of the formula (1). The compositions according to the invention can, in addition to the compounds according to the invention, also comprise other additives, for example antioxidants or light protection agents.

[0055] Incorporation into the organic polymers, for example into the synthetic organic, in particular thermoplastic, polymers can take place by adding the hydroxydiphenyl ether compound according to the invention and, if desired, other additives by the methods customary in the art. Incorporation can expediently take place before or during shaping, for example by mixing the pulverulent components or by adding the antimicrobial active substance to the melt or solution of the polymer, or by applying the dissolved or dispersed compounds to the polymer, if desired with subsequent evaporation of the solvent. Another method of incorporating the mixtures according to the invention into polymers involves adding the former before or during polymerization of the corresponding monomers or before crosslinking.

[0056] The mixtures according to the invention can also be added to the organic polymers to be finished in the form of a masterbatch which comprises these compounds, for example, in a concentration of from 2.5 to 25% by weight.

[0057] The resulting antimicrobially finished polymer compositions can be converted into shaped articles, for example fibres, films, tapes, sheets, multi-wall sheets, containers, tubes and other profiles, by conventional methods, for example by hot pressing, spinning, extrusion or injection moulding.

[0058] The hydroxydiphenyl ether compounds of the formula (1) are also suitable for the antimicrobial finishing of undyed and dyed or printed fibre materials made, for example, of silk, wool, polyamide, polyester or polyurethane, and in particular of cellulosic fibre materials of all types. Examples of such fibre materials are the natural cellulose fibres, such as cotton, linen, jute and hemp, and also pulp and regenerated cellulose. The hydroxydiphenyl ether compounds according to the invention are also suitable for the antimicrobial finishing of hydroxyl-group-containing fibres which are present in mixed fabrics, for example, of mixtures of cotton with polyester fibres or polyamide fibres. The hydroxydiphenyl ether compounds of the formula (1) are also suitable for incorporation into non-wovens.

[0059] "Non-woven" is a type of fabric that is not spun and woven into a cloth, but instead bonded together. According to the ISO definition it is a manufactured sheet, web, or batt of directionally or randomly orientated fibres, bonded by friction, and/or adhesion.

[0060] Nonwoven textiles are widely used in disposable as well as durable goods, such as baby diaper, feminine hygiene, adult incontinence, wipers, bed linings, automotive industries, medical face masks, air and water filtration, home furnishing and geotextiles. Such materials can be fabricated by different techniques, such as spunbonding, melt blown, carded thermal bonding and carded chemical bonding, dry and/or wet laid and needlefelts. Because of the nature of such applications, increasingly the market is demanding products with specific properties such as antimicrobial efficacy.

[0061] For this purpose, one or more compounds of the formula (1) are advantageously applied to the textile fibre material in an amount of from 0.01 to 20% by weight, preferably 0.1-3% by weight, and in particular from 0.25 to 2% by weight, based on the weight of the fibre material, in a process analogous to dyeing.

[0062] The hydroxydiphenyl ether compounds according to the invention can be applied to the fibre material and fixed to the fibre in different ways, in particular in the form of aqueous dispersions or printing pastes.

[0063] The textile fibre materials finished using the compounds of the formula (1) according to the invention have an excellent and long-lasting antimicrobial protection.

[0064] An antimicrobial textile treatment formulation has, for example, the following composition:

20% by weight of a compound of formula (1)

5% by weight of sodium lauryl sulfate
 10% by weight of an ethoxylated fatty alcohol
 40% by weight of propylene glycol and
 25% by weight of water.

[0065] The hydroxydiphenyl ether compounds according to the invention can be also be used in paper finishing, printing thickeners containing starch, varnishes and paints.

[0066] The hydroxydiphenyl ether compounds according to the invention are also useful for the disinfection and general antimicrobial treatment, such as deodorising, of the skin, mucous membrane and hair, preferably for the disinfection of hands and wounds. The hydroxydiphenyl ether compounds according to the invention are useful for the preservation of cosmetic and household products against microbial spoilage.

[0067] Therefore, these compounds are suitable as an antimicrobial active substance in personal care products as shampoos, bath- and shower additives, hair-care products, liquid and bar soaps, lotions and cremes, deodorants, other aqueous or alcoholic solutions, for example cleaning solutions for the skin, moist cleaning sheets, oils and powders.

[0068] A further subject of the present invention is therefore a personal care composition comprising at least one compound of the formula (1) and cosmetically tolerable carriers or auxiliaries.

[0069] The personal care composition according to the present invention comprises 0.01 to 15, preferably 0.5 to 10 % b.w. of the hydroxydiphenyl ether compounds of formula (1) and cosmetically tolerable carriers or auxiliaries.

[0070] The personal care composition according to the invention can be formulated as a water-in-oil or oil-in-water emulsion, as an oil-in-alcohol lotion, as a vesicular dispersion of an ionic or non-ionic amphiphilic lipid, as a gel, solid stick, aerosol formulation or a surfactant based formulation, such as a soap or skin cleanser.

[0071] As a water-in-oil or oil-in-water emulsion, the cosmetically compatible auxiliary preferably contains 5 to 50% of an oil phase, 5 to 20% of an emulsifier and 30 to 90% of water. The oil phase can in this case contain any oil suitable for cosmetic formulations, e.g. one or more hydrocarbon oils, a wax, a natural oil, a silicone oil, a fatty acid ester or a fatty alcohol. Preferred mono- or polyols are ethanol, isopropanol, propylene glycol, hexylene glycol, glycerol and sorbitol.

[0072] Any conventionally usable emulsifier can be used for the cosmetic composition according to the invention, for example one or more ethoxylated esters of natural derivatives, e.g. polyethoxylated esters of hydrogenated castor oil; or a silicone oil emulsifier, e.g. a silicone polyol; an optionally ethoxylated fatty acid soap; an ethoxylated fatty alcohol; an optionally ethoxylated sorbitan ester; an ethoxylated fatty acid; or an ethoxylated glyceride.

[0073] The cosmetic composition may also comprise further components, e.g. emollients, emulsion stabilisers, skin humectants, skin tanning accelerators, thickeners, such as xanthan, moisture-retention agents, such as glycerol, preservatives, perfumes and colourings.

[0074] The preparation of the cosmetic composition can be effected by physically mixing the antimicrobial(s) with the auxiliary by customary methods, for example by simply stirring the individual components together.

[0075] Cosmetic formulations include a very wide range of cosmetic products. Suitable products are, for example, especially the following:

- skin-care products, for example skin washing and cleansing products in the form of bars of soap or liquid soaps, syndets or washing pastes;
- bath products, for example liquid (foam baths, milks, shower products) or solid bath products, such as bath pearls and bath salts;
- skin-care products, such as skin emulsions, multiple emulsions or skin oils;
- decorative body-care products, for example face make-ups in the form of day or powder creams, face powders (loose and compressed), rouge or cream make-ups, eye-care products, for example eye shadow products, mascara, eyeliners, eye creams or eye-fix creams; lip-care products, for example lipstick, lip gloss, lip liner, nail-care products, such as nail varnish, nail varnish remover, nail hardeners or cuticle removers;
- feminine hygiene products, such as feminine hygiene washing lotions or sprays;
- foot-care products, for example foot baths, foot powders, foot creams or foot balms, special deodorants and antiperspirants or products for scrubbing off callouses;
- sunscreens, such as sun milks, lotions, creams, oils, sunblockers or tropicals, pre-sun products or after-sun products;
- suntanning products, for example self-tanning creams;
- depigmenting products, for example products for bleaching or lightening skin;
- insect repellents, for example insect oils, lotions, sprays or sticks;
- deodorants, for example deodorant sprays, non-aerosol sprays, deodorant gels, sticks or roll-ons;
- antiperspirants, for example antiperspirant sticks, creams or roll-ons;
- products for cleansing and treating impure skin, for example syndets (solid or liquid), peeling or scrubbing products

or peeling masks;

- chemical depilatory products, for example depilatory powders, liquid depilatory products, creamy or pasty depilatory products, depilatory gels or aerosol foams;
- shaving products, for example shaving soap, foaming shaving creams, non-foaming shaving creams, shaving foams and gels, preshaving products for dry shaving, after-shaves or aftershave lotions;
- scents, for example perfumes (Eau de Cologne, Eau de Toilette, Eau de Parfum, Parfum de Toilette, perfume), perfume oils or perfume creams;
- products for oral and dental hygiene as well as for dentures, for example toothpastes, tooth gels, tooth powders, mouth-wash concentrates, anti-plaque mouth-washes, denture cleaning products or denture adhesion products;
- cosmetic formulations for hair treatment, for example hair washes in the form of shampoos, hair conditioners, hair-care products, for example pretreatment products, hair tonics, hair styling creams and gels, pomades, hair rinses, deep conditioning treatments, intensive hair care treatments, hair setting products, for example waving agents for perms (hot wave, mild wave, cold wave), hair straightening products, liquid hair fixatives, hair foams, hair sprays, bleaching agents, for example hydrogen peroxide solutions, bleaching shampoos, bleaching creams, bleaching powders, bleaching pastes or oils, temporary, semitemporary or permanent hair dyes, products containing self-oxidising dyes, or natural hair dyes, such as henna or camomile.

[0076] An antimicrobial soap has, for example, the following composition:

0.01 to 5% by weight of a compound of the formula (1)
 0.3 to 1 % by weight of titanium dioxide
 1 to 10% by weight of stearic acid
 to 100% of soap base, for example the sodium salts of tallow fatty and coconut fatty acid or glycerols.

[0077] A shampoo has, for example, the following composition:

0.01 to 5% by weight of a compound of the formula (1)
 12.0% by weight of sodium laureth-2-sulfate,
 4.0% by weight of cocamidopropylbetaine,
 3.0% by weight of NaCl and
 water to 100%.

[0078] A deodorant has, for example, the following composition:

0.01 to 5% by weight of a compound of the formula (1)
 60% by weight of ethanol,
 0.3% by weight of perfume oil and
 water to 100%.

[0079] The personal care formulations listed above can be in a very wide range of forms of presentation, for example

- in the form of liquid formulations as an O/W emulsion,
- in the form of a gel,
- in the form of an oil, cream, milk or lotion,
- in the form of a powder, lacquer, pellets or make-up,
- in the form of a stick,
- in the form of a spray (spray with propellant or pumping spray) or an aerosol,
- in the form of a foam, or
- in the form of a paste.

[0080] The oral hygiene composition may comprise an additional antibacterial enhancing agent, for example an anionic polymeric polycarboxylate, a dehydrated polyphosphate salt, a compound which provides a source of fluoride ions, a polishing material, including siliceous material or sodium bicarbonate, an orally acceptable vehicle, including a water-phase with humectant, thickeners, surface-active agents and a flavoring or sweetening material.

[0081] The oral hygiene composition according to the invention contains from 0.003 to 5 % by weight based on the total weight of the composition, of antimicrobial or a mixture of antimicrobials.

[0082] The preparation of the oral hygiene composition can be effected by physically mixing the antimicrobial(s) with the other ingredients by customary methods, for example by simply stirring the individual components together, then

mixing further under vacuum.

[0083] An oral care formulation has, for example, the following composition:

10% by weight of Sorbitol,
 10% by weight of Glycerin,
 15% by weight of Ethanol,
 15% by weight of Propylene glycol,
 0.5% by weight of Sodium lauryl sulfate,
 0.25% by weight of Sodium methyl cocyl taurate,
 0.25% by weight of Poloxypropylene/polyoxyethylene block copolymer,
 0.10% by weight of Mint flavor,
 0.3% by weight of a compound of formula (1),
 48.6% by weight of water.

[0084] The oral hygiene composition may be in various forms of presentation including the form of a gel, paste, cream or mouthwash.

[0085] Furthermore the hydroxydiphenyl ether compounds according to the invention are useful as household cleaners for the cleaning and disinfection of hard surfaces.

[0086] A detergent has, for example, the following composition:

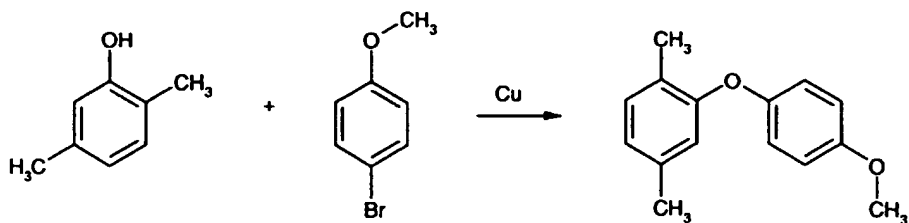
0.01 to 5% by weight of a compound of the formula (1)
 3.0% by weight of Octanol 4EO,
 1.3% by weight Fatty alcohol C₈-C₁₀ Polyglucoside,
 3.0% by weight Isopropanol,
 water to 100%.

[0087] A better understanding of the present invention and of its many advantages will be had by referring to the following Examples, given by way of illustration.

Example 1

Reaction scheme first reaction step:

[0088]



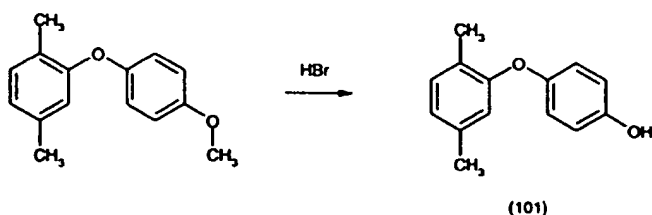
(101a)

[0089] The mixture of 6.1 g (0.05 mol) 2,5-Dimethylphenol, 2.8 g (0.05 mol) KOH, 0.4 g (0.006 mol) copper powder and 50 g (0.25 mol) bromo anisole is heated in a standard reaction apparatus, equipped with a water trap, to 160 °C for 5 h. After cooling the reaction mass is suspended in toluene and filtrated. After distilling off the solvent and excess reagent the product of formula (101 a) is isolated by distillation at 125 °C/0.01 mbar.

[0090] A colourless oil is obtained, slowly crystallizing at room temperature. Yield: 4.6 g (40 %)

Reaction scheme second reaction step:

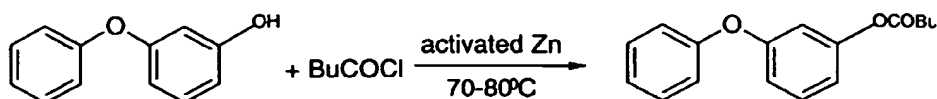
[0091]



[0092] 4.6 g (0.02 mol) of 4-(2,5-Dimethylphenoxy)-methoxybenzol and 30 ml HBr (47 % solution in water) are heated to reflux in 100 ml acetic acid for 4 h. After cooling and distilling off acetic acid the reaction mass is dissolved in 100 ml methylene chloride and washed with 200 ml water with pH adjusted to pH 10 with 10 % NaOH. Product of formula (101) is isolated from the organic phase by distillation at 160 °C/0.01 mbar. Yield: 2.2 g (52 %)

Example 2Reaction scheme first reaction step:

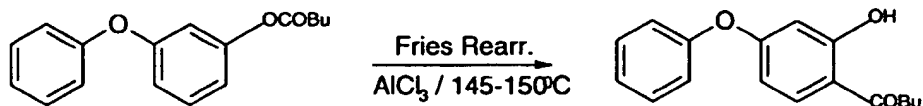
[0093]



[0094] Into a three necked flask equipped with overhead stirrer & condenser was charged Acid chloride [57.25m. moles], Toluene [250ml] & activated zinc [57.24m.moles]. This mixture stirred at room temperature [30°C], for 15minutes. m-Phenoxyphenol [4.5g. 24.20m.moles] in Toluene [150ml], was added and the reaction mixture stirred at 70-75°C for 30minutes. TLC showed the absence of starting material. Reaction mixture cooled to room temperature & filtered. Organic layer washed with 2x100ml of aqueous solution [20%] of Potassium carbonate followed by water wash. It was briefly dried over anhydrous sodiumsulphate and solvent distilled under reduced pressure to get O-Acyl compound. Yield 85%.

Reaction scheme second reaction step:

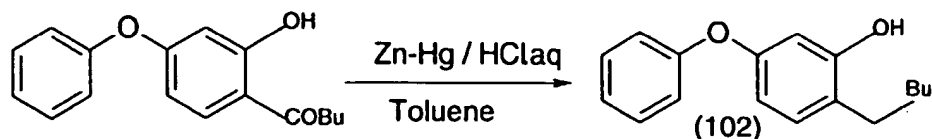
[0095]



[0096] O-Acetate [16m.moles], Aluminium chloride [20m.moles], were mixed together and heated to 145-50°C for 3 to 4 hrs. protected from moisture. TLC after 4hrs showed the absence of starting material. Reaction mixture was cooled to room temperature and poured to dil. hydrochloric acid and extracted with 2x50ml of dichloromethane. Organic extract washed with water until the washings are neutral to litmus. Solvent distilled off and the residue chromatographed over silicagel using hexane:ethylacetate [98:2] as eluent. Yield of 2-Acylphenol is 72%.

Reaction scheme third reaction step:

[0097]



[0098] Amalgamated Zinc [12g], prepared according to standard procedures was transferred to a three necked round bottomed flask provided with a over head stirrer and a reflux condenser. Water [10ml], Conc.Hydrochloric acid [20ml] were added followed by 2-Acyl phenol [10m.moles] dissolved in 20ml toluene. Ethanol [2ml], was added the reaction mixture stirred and refluxed. Conc.Hydrochloric acid [3to 4ml], was added after every 3-4hrs of reflux. Heating stopped after 24hrs of reflux. [TLC after 24hrs of reflux indicated the presence of Starting material. Addition of further quantity of Zinc amalgam did not help]. Organic material extracted with 2x35ml toluene and the extracts washed with water until washings neutral to litmus. Solvent distilled off under reduced pressure and the residue chromatographed over silicagel, using Hexane : Ethylacetate [97:3] as the eluent, to obtain the pure product of formula (102).
Yield , 50-55%.

Example 3:

[0099] An agar incorporation test is carried out to determine the MIC of various compounds shown in table 1

Medium: Nutrient agar as test agar for bacteria:
Mueller hinton agar to cultivate the aerobic bacteria
Mueller hinton bouillon for obtaining the suspension of microorganisms
Ethanol as solvent
Wilkins-Chalgren agar to cultivate the aerobic bacteria
Sabouraud glucose agar to cultivate the dermatophytes

Examples of Test bacteria: Staphylococcus aureus ATCC 6538
Staphylococcus hominis DSM 20330
Escherichia coli NCTC 8196
Pseudomonas aeruginosa CIP A-22
Candida albicans ATCC 10231
Aspergillus niger ATCC 6275

Procedure: The test substances are dissolved in ethanol, and a dilution series of the compound of the formula (102) in agar are prepared.
Anaerobic bacteria and dermatophytes are activated on agar-plates, and washes off with Mueller-Hinton bouillon. Aerobic bacteria are activated in Mueller-Hinton bouillon overnight. The test germ suspension are diluted with Mueller-Hinton bouillon to a density of McFarland standard 0.5.
10 µl of each germ suspension is dropped onto the agar plates containing the test substance, and the plates are then incubated at 37°C for 2 days. (Aerobic bacteria are incubated at 36°C for 72 hours, anaerobic bacteria are incubated at 30°C for 72 hours). As controls, the bacterial suspensions are applied to agar plates without test substances. In order to exclude the solvent ethanol having an influence on the growth properties, the bacterial suspensions are applied to agar plates containing ethanol, but without test substance.
After the plates have been incubated, the growth of the bacteria on the test-substance-containing plates is compared with that on the control plates.
The minimum inhibitory concentration (MIC) is given as the lowest concentration which shows clear inhibition compared with the control.

[0100] The MIC values are given in the table 1 below.

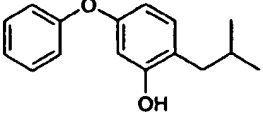
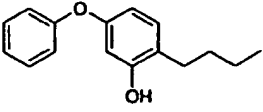
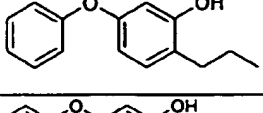
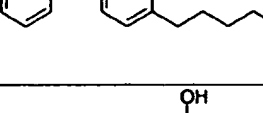
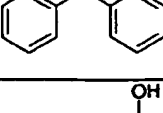
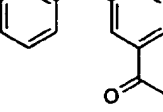
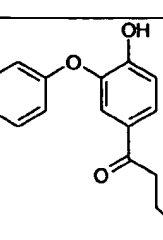
Table 1: Minimum Inhibitory Concentration [ppm]							
Comp. of formula	Test Organism						
	Structure	SH	EC	CA	AN	SA	PA
(103)		30	30	30	120		
(104)		30	30	30	60		
(105)		30	30	30	30		
(106)		30	30	60	60		
(107)		30	30	0	120		
(108)		60	120	0	0		
(109)		30	30	120	120		

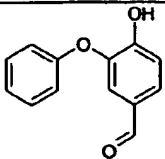
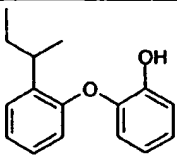
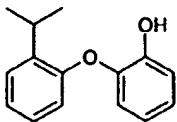
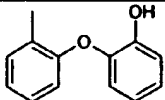
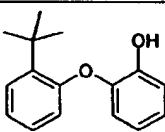
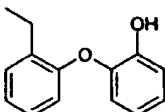
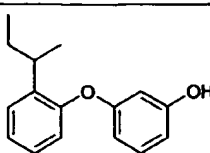
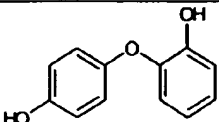
Table 1: Minimum Inhibitory Concentration [ppm]							
Comp. of formula	Test Organism						
	Structure	SH	EC	CA	AN	SA	PA
(110)		0	30	0	0		
(111)		60	0	30	120		
(112)		60	0	60	120		
(113)		30	30	120	60		
(114)		30	30	60	120		
(115)		120	120	120	120		
(116)		30	0	30	30		
(117)		0	60	0			0

Table 1: Minimum Inhibitory Concentration [ppm]

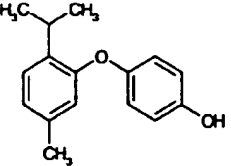
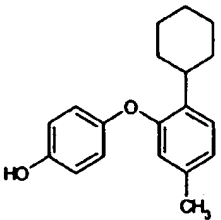
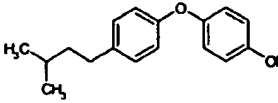
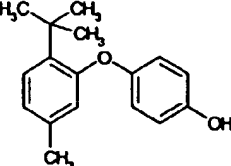
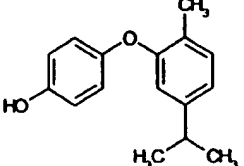
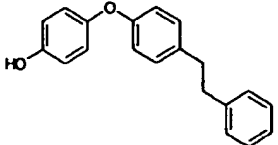
Comp. of formula	Test Organism						
	Structure	SH	EC	CA	AN	SA	PA
(118)		3	50	50		5	0
(119)		3	0	0		3	0
(120)		4	0	0			0
(121)		5	0	13		7	0
(122)		6	0	13		6	0
(123)		8	0	0			0

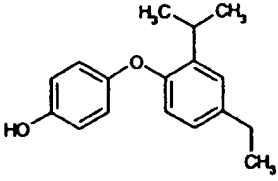
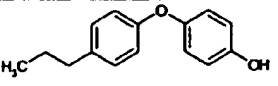
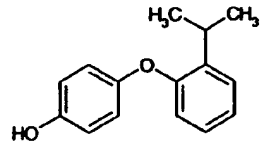
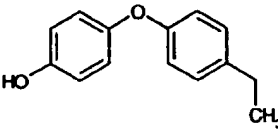
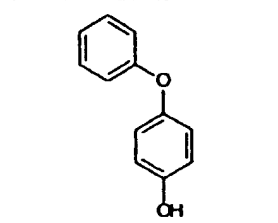
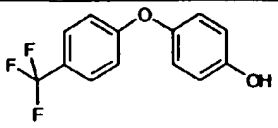
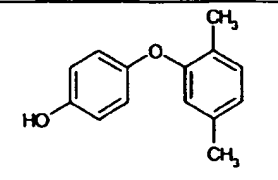
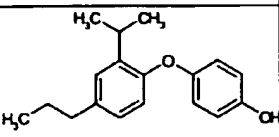
Table 1: Minimum Inhibitory Concentration [ppm]							
Comp. of formula	Test Organism						
	Structure	SH	EC	CA	AN	SA	PA
(124)		8	0	60			0
(125)		30	120	30			0
(103)		30	0	60			0
(126)		120	120	120			0
(127)			100	50		500	50
(128)			50	50		50	50
(129)			0	25		50	25

Table 1: Minimum Inhibitory Concentration [ppm]							
Comp. of formula	Test Organism						
	Structure	SH	EC	CA	AN	SA	PA
(130)			0	20		50	20

SA = *Staphylococcus aureus* ATCC 6538

SH = *Staphylococcus hominis* DSM 20328

EC = *Escherichia coli* NCTC 8196

PA = *Pseudomonas aeruginosa* CIP A-22

CA = *Candida albicans* ATCC 10231

AN = *Aspergillus niger* ATCC 6275

[0101] The results in the above table clearly show that the compounds have antimicrobial activity.

Example 4: Preparation of specific diphenylether compounds

[0102] The following compounds listed in table 2 are prepared by the methods described in detail below:

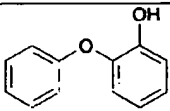
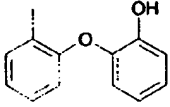
Table 2:					
Comp. of form.	Structure	Name / CAS	Synthetic procedure employed	MP [°C]	Technique used for structure assignment
(107)		2-Phenoxyphenol 2417-10-9	Procedure I & IV	98	1. ¹ H-NMR 2. M.S.
(113)		2-(2-Methyl) phenoxy-phenol 26321-31-3	Procedure I & IV	—	1. ¹ H-NMR 2. M.S.

Table 2:

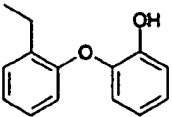
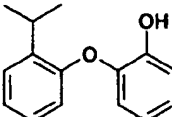
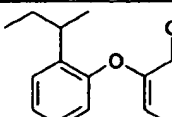
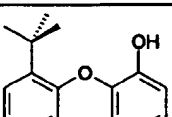
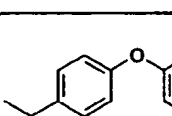
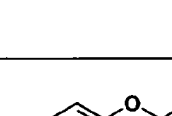
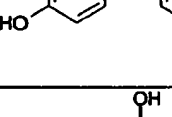
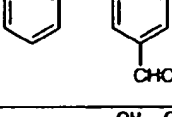
Comp. of form.	Structure	Name / CAS	Synthetic procedures employed	MP [°C]	Technique used for structure assignment
(115)		2-(2-Ethyl) phenoxyphenol 137610-67-4	Procedure I & IV	—	1. ¹ H-NMR 2. M.S.
(112)		2-(2-Isopropyl)- phenoxyphenol.	Procedure I & IV	—	1. ¹ H-NMR 2. M.S.
(111)		2-(2-sec-Butyl)- phenoxyphenol	Procedure I & IV	—	1. ¹ H-NMR 2. M.S.
(114)		2-(2-tert-Butyl)- phenoxyphenol	Procedure I & IV	—	1. ¹ H-NMR 2. M.S.
(131)		2-(4-Isopropyl)- phenoxyphenol	Procedure I & IV	—	1. ¹ H-NMR 2. M.S.
(117)		2-(4-Hydroxy phenoxy)phenol. 23990-90-1	Procedure I & IV	155	1. ¹ H-NMR 2. M.S.
(110)		4-Hydroxy-3-phenoxy- benzaldehyde	Procedure I & IV	118 - 120	1. ¹ H-NMR 2. M.S.
(109)		2-Butanoyl-6- phenoxyphenol	Procedure I, IV & VI A.	—	1. ¹ H-NMR 2. M.S.

Table 2:

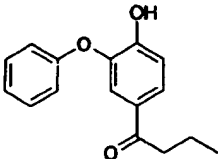
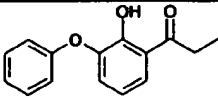
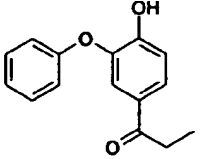
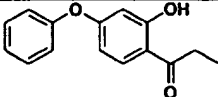
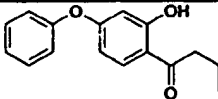
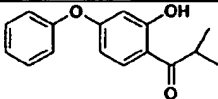
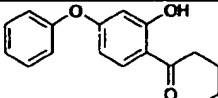
Comp. of form.	Structure	Name / CAS	Synthetic procedure employed	MP [°C]	Technique used for structure assignment
		4-Butanoyl-6-phenoxyphenol.			
(108)	 	2-Propanoyl-6-phenoxyphenol 4-Propanoyl-6-phenoxyphenol	Procedure I, IV & VI A.	94-97	1. ¹ H-NMR 2. M.S.
(132)		2-Propanoyl-5-phenoxyphenol	Procedure V, VI A / VI B.	—	1. ¹ H-NMR 2. M.S.
(133)		2-Butanoyl-5-phenoxyphenol	Procedure V, VI A / VI B	72-73	1. ¹ H-NMR 2. M.S.
(134)		2-(2-methyl-propanoyl)-5-phenoxyphenol	Procedure V, VI A / VI B.	63-65	1. ¹ H-NMR 2. M.S.
(135)		2-Pentanoyl-5-phenoxyphenol	Procedure V, VI A / VI B.	—	1. ¹ H-NMR 2. M.S.

Table 2:

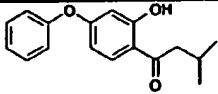
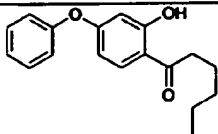
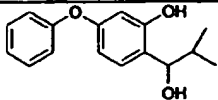
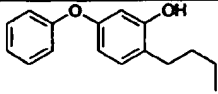
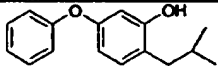
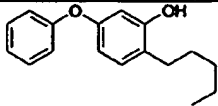
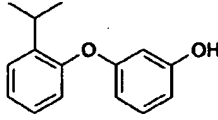
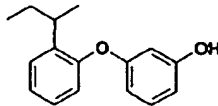
Comp. of form.	Structure	Name / CAS	Synthetic procedures employed	MP [°C]	Technique used for structure assignment
(136)		2-(3-Methyl butanoyl)- 5-phenoxyphenol	Procedure V, VI A / VI B.	53- 54	1. ¹ H-NMR 2. M.S.
(137)		2-Hexanoyl-5- phenoxyphenol	Procedure V, VI A / VI B.	—	1. ¹ H-NMR 2. M.S.
(138)		2-(1-Hydroxy-2- methylpropyl)-5- phenoxyphenol	NaBH ₄ reduction of '16'	—	1. ¹ H-NMR 2. M.S.
(104)		2-Butyl-5-phenoxy- phenol	Procedure V, VI A / VI B & III / IV.	—	1. ¹ H-NMR 2. M.S.
(103)		2-(2-Methylpropyl)-5- phenoxyphenol	Procedure V, VI A / VI B & III / VII.	—	1. ¹ H-NMR 2. M.S.
(106)		2-Pentyl-5-phenoxy- phenol	Procedure V, VI A / VI B & III / VII	—	1. ¹ H-NMR 2. M.S.
(139)		3-(2-Isopropyl)- phenoxyphenol	Procedure I & IV	—	1. ¹ H-NMR 2. M.S.
(116)		3-(2-sec-Butyl) phenoxyphenol	Procedure I & IV	—	1. ¹ H-NMR 2. M.S.

Table 2:

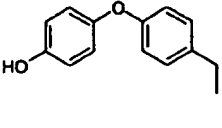
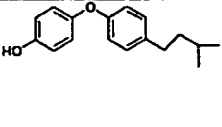
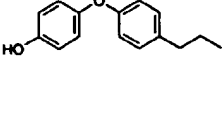
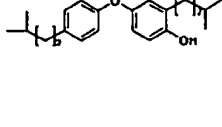
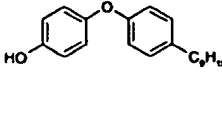
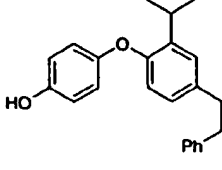
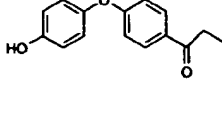
Comp. of form.	Structure	Name / CAS	Synthetic proceduree mployed	MP [°C]	Technique used for structure assignment
(126)		4-(4-Ethyl phenoxy)- phenol	Procedure I & IV	—	1. ¹ H-NMR 2. M.S.
(140)		4-(4-(3-Methyl butyl)- phenoxy) phenol 35065-13-5	Procedure I & IV	---	1. ¹ H-NMR 2. M.S.
(125)		4-(4-Propyl phenoxy)- phenol	Procedure I, II, IV & III / VII	----	1. ¹ H-NMR 2. M.S.
(141)		4-((3-Methyl butyl)- phenoxy)3-(3-methyl butyl)phenol	Procedure I, II, IV & III / VII	-----	1. ¹ H-NMR 2. M.S.
(142)		4-(4-Nonyl phenoxy)- phenol	Procedure I, II, IV & III / VII	50- 51	1. ¹ H-NMR 2. M.S.
(143)		4-(2-Methylethyl-4-(2- phenylethyl)phenoxy)- phenol	Procedure I, II, IV & III / VII	---	1. ¹ H-NMR 2. M.S.
(144)		4-(4-Propionyl phenoxy)phenol	Procedure I, II & IV	—	1. ¹ H-NMR 2. M.S.

Table 2:

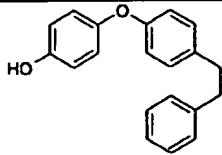
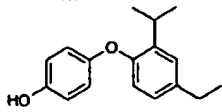
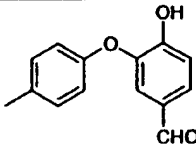
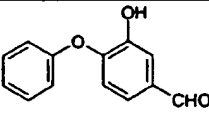
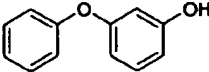
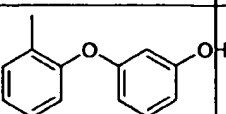
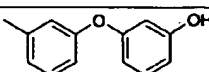
Comp. of form.	Structure	Name / CAS	Synthetic procedurree mployed	MP [°C]	Technique used for structure assignment
(145)		4-(4-(2-Phenyl ethyl)- phenoxy)phenol	Procedure I , II, IV & III / VII	84- 86	1. ¹ H-NMR 2. M.S.
(146)		4-(4-ethyl -2- methylethyl-)phenoxy)- phenol	Procedure I , II IV & III / VII	---	1. ¹ H-NMR 2. M.S.
(147)		4-Hydroxyl-5-(4- methylphenoxy) benzaldehyde 136805-20-4	Procedure I & IV	88- 90	1. ¹ H-NMR 2. M.S.
(148)		3-Hydroxyl-4-phenoxy benzaldehyde 35065-13-5	Procedure I & IV	---	1. ¹ H-NMR 2. M.S.
(149)		3-phenoxyphenol 713-68-8	Procedure V	---	1. ¹ H-NMR 2. M.S.
(150)		3-(2-methyl phenoxy)phenol	Procedure I & IV	---	1. ¹ H-NMR 2. M.S.
(151)		3-(3-methyl phenoxy)phenol	Procedure I & IV	---	1. ¹ H-NMR 2. M.S.

Table 2:

Comp. of form.	Structure	Name / CAS	Synthetic proceduree mployed	MP [°C]	Technique used for structure assignment
(105)		2-Propyl-5-phenoxyphenol	Procedure V, VI A /VI B & III /VII	---	1. ¹ H-NMR 2. M.S.
(152)		2-Propyl-5-(2-methylphenoxy)phenol	Procedure I, IV, VI A /VI B & III /VII	--	1. ¹ H-NMR 2. M.S.
(153)		2-Propyl-5-(3-methylphenoxy)phenol	Procedure I, IV, VI A /VI B & III /VII	---	1. ¹ H-NMR 2. M.S.
(154)		5-phenoxy-2-(3-methylbutyl)phenol	Procedure V, VI A /VI B & III /VII	---	1. ¹ H-NMR 2. M.S.
(155)		2-(3-methylbutyl)-5-(3-methylphenoxy)phenol	Procedure I, II, IV & III /VII	---	1. ¹ H-NMR 2. M.S.
(156)		2-Hexyl-5-phenoxyphenol	Procedure V, VI A /VI B & III /VII	----	1. ¹ H-NMR 2. M.S.
(157)		2-(2-phenylethyl)- 5-phenoxy phenol	Procedure V, VI A /VI B & III /VII	73-75° C	1. ¹ H-NMR 2. M.S.
(158)		2-(2-phenylethyl)- 5-(2-methyl phenoxy)phenol	Procedure I, IV, VI A /VI B & III /VII	-----	1. ¹ H-NMR 2. M.S.

Table 2:

Comp. of form.	Structure	Name / CAS	Synthetic proceduree mployed	MP [°C]	Technique used for structure assignment
(159)		2-(2-phenylethyl)- 5-(3-methyl phenoxy) phenol	Procedure I, IV, VI A /VI B & III /VII	---	1. ¹ H-NMR 2. M.S.
(160)		2-Dodecanoyl- 5-phenoxy phenol	Procedure V, VI A /VI B & III /VII	---	1. ¹ H-NMR 2. M.S.
(161)		3-[4-(2-methyl ethyl)]phenoxy phenol	Procedure I & IV	---	1. ¹ H-NMR 2. M.S.
(162)		4-(2-methylethyl-4-ethyl)phenoxy phenol	Procedure I, II, IV & III /VII	---	1. ¹ H-NMR 2. M.S.
(127)		4-phenoxy phenol 831-82-3	Procedure I & IV	76-77	1. ¹ H-NMR 2. M.S.
(163)		4-(4-hydroxy) phenoxy phenol 1965-09-9	Procedure I & IV	---	1. ¹ H-NMR 2. M.S.
(164)		3-(4-hydroxy) phenoxy phenol 68100-19-6	Procedure I & IV	116-118	1. ¹ H-NMR 2. M.S.

General Synthesis of HydroxydiphenylethersGeneral Procedure-I.Example :

[0103] Ullmann condensations are carried out as per the procedure outlined by R.G.R.Bacon and O.J. Stewart, J. Chem. Soc., 1965 4953.

[0104] To a stirred solution of o-cresol 21.6 g. (0.2 mol) in 110 ml N, N-dimethylacetamide under nitrogen atmosphere, was added o-bromoanisole 74.8 g (0.4 mole) followed by Cuprous oxide 28.62 g (0.4 mole). Reaction mixture refluxed for 24 hr at 165-167°C. It was cooled to room temperature and poured to 1l water containing 100 ml concentrated HCl. Reaction mixture extracted with 3x150 mL ether. Organic extract washed with 10% NaOH solution to remove unreacted cresol. Solvent and excess of o-bromoanisole distilled off under reduced pressure.. Product purified by chromatography over silica gel column.

yield = 28 g.

% yield by theory = 65%

[0105] General catalysts for Ullmann condensation: Cu, Cu₂Cl₂, bas. CuCO₃, CuCl₂, CuO, Cu₂O, reaction in high boiling solvents as Pyridin, DMF, DMA, DMSO, Toluene, Xylene and others, bases are hydroxides/carbonates from group 1/2 metals

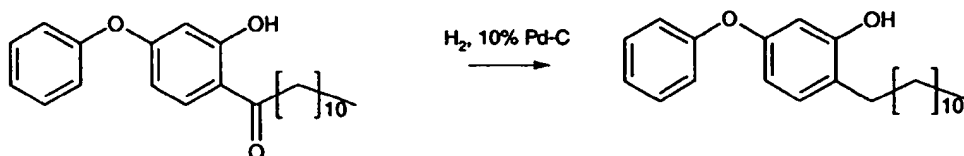
General procedure - IIExample :Acylation of methoxy diphenyl ether.

[0106] Isovelaroyl chloride 1.2g (0.01 mole) and ethylene dichloride (10ml) were mixed and cooled to 0°C with stirring. Anhydrous AlCl₃ 2.7g (0.02mole) added portionwise maintaining temp. below 5°C. p-Methoxy diphenyl ether 2g (0.01m) added dropwise during 15 minutes. Stirring continued for 1 hr at 0 - 5°C. Reaction mixture added to 100 ml of cold water with vigorous stirring, followed by extraction with 50 ml ethylene dichloride. Organic layer separated, washed with 50 ml water and dried briefly over anhy. Na₂SO₄. Solvent distilled under reduced pressure to get the crude product. It was purified over silica gel column using hexane:ethyl acetate as eluent.

Yield: 2.46 g.

% yield by theory: 85-90%

[0107] General Friedl-Crafts acylation catalysts: Lewis acids as AlCl₃, ZnCl₂, FeCl₃, BCl₃, BF₃, transition metal trifluorosulfonates (eg. Sc(OTf)₃) reaction in inert solvents as EDC, CH₂Cl₂, CS₂, Nitrobenzene

General Pcedure - IIIExample :[0108]Hydrogenation of Keto to methylene.

[0109] To a 125 ml autoclave, a solution of Keto compound 3.67g (0.01 mole) in 50 ml ethanol was charged, followed by 10ml gl. acetic acid, 10%Pd-C (5mg), 0.1 ml perchloric acid and flushed twice with hydrogen. Reaction mixture hydrogenated at an autoclave temp. of 65°C and pressure of 100-110 psi for 4-6 hr. Completion of the reaction was followed by TLC. Reaction mixture cooled to room temperature, pressure released and filtered. Filtrate was added to

200 ml water. Ethylene dichloride (100 ml) was added, organic layer washed with 2x50 ml 5% NaHCO_3 solution and dried over anhy. Na_2SO_4 . Solvent distilled off under reduced pressure to get the product.

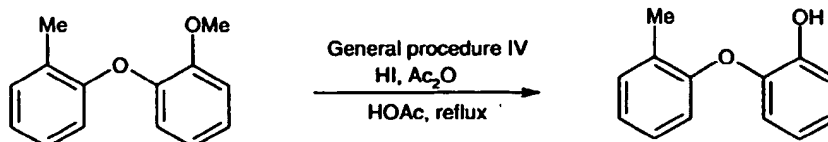
Yield: 3.33 g.

% yield by theory: 90-95%

General procedure - IV

Example:

[0110]



Demethylation of methoxy ether to phenol.

[0111] Methyl ether 14 g (0.065 mole), acetic acid 25 ml, hydroiodic acid 25 ml, acetic anhydride 20 ml. were mixed and refluxed under stirring at 105-110°C for 1 hr. Reaction mixture poured into 1 L ice cold water, decolorized with Sodium sulphite solution, neutralized with saturated NaHCO_3 Solution (2x100 ml) and extracted with DCM (3X100 ml). Organic layer washed with water, dried over Na_2SO_4 . Crude reaction mixture chromatographed over silica column to get the pure product.

Yield: 10 g

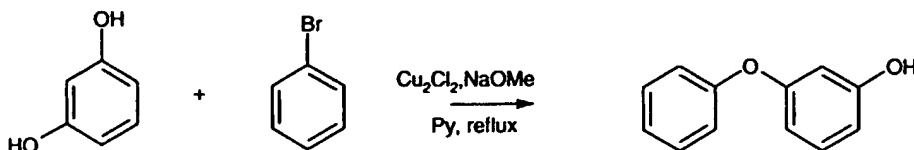
% yield by theory: 75%

[0112] General demethylating agents as AlCl_3 , BCl_3 , BF_3 , HBr, pyridinium x HCl

General procedure - V

Example :

[0113]



Preparation of m-phenoxyphenol

[0114] To a stirred solution of 49.5 g (0.45 mol) of resorcinol in 75 ml dry pyridine under nitrogen atmosphere, 16.2 g (0.3 mol) of Sodium methoxide was added. Heating started and methanol fractionally distilled off over a period of 0.5 hr. Bromobenzene, 142 g (0.9 mole) was run in to the reaction mixture followed by 2.2 g, of Cuprous chloride. Reaction mixture heated under reflux for 3-4 hr, pyridine distilled off while the pot temperature rose to 150°C. The residue was poured into 50 ml conc. HCl in 120 ml water and stirred. Organic material extracted in 200 ml benzene followed by washing with 25 ml of 20% HCl. Organic layer extracted with 100 ml of 10% NaOH solution followed by a second extraction with 20 ml of 10% NaOH. The combined aqueous extracts were acidified with, HCl_{conc} , liberated m-phenoxyphenol was extracted into benzene (300 ml). From the organic layer benzene was removed by distillation. Crude product purified by filtration over a column of silica.

Yield: 35 g

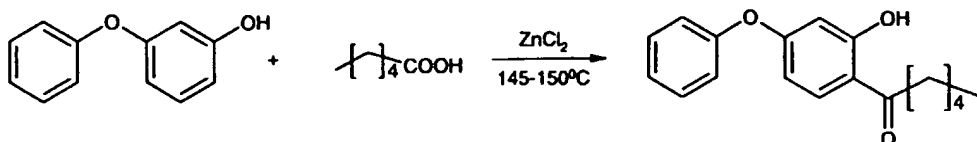
% yield by theory: 40-42%

Catalysts for Ullmann condensation see Proc. I

General procedure - VI - A

Example :

[0115]



Acylation of m-phenoxy phenol

[0116] Hexanoic acid 12.87g (0.11 mole) added to fused ZnCl_2 6.50g (0.15 mol), dissolved at 145-150°C. To the above reaction mixture m-phenoxy phenol 5.9g (0.032 mol) was added.

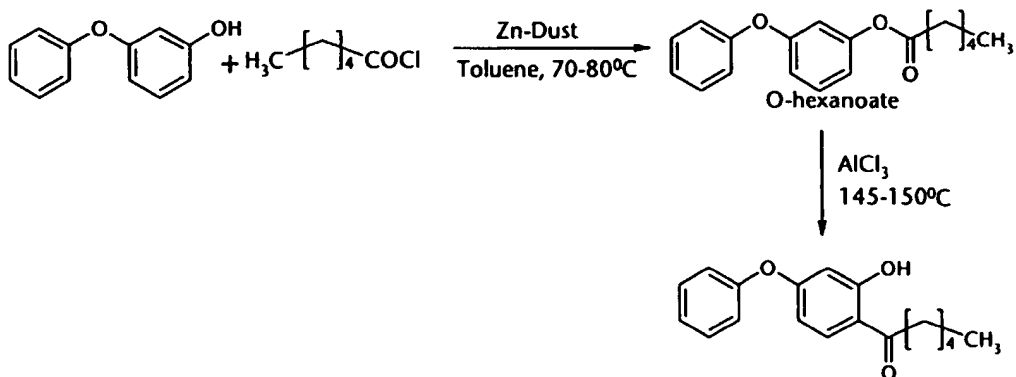
[0117] Reaction mass stirred at 145-150°C for 3 hr. It was cooled to room temperature and poured over 250 ml cold water, washed with sat. NaHCO_3 solution (2x150ml), extracted with ethyl acetate (2x100 ml). Organic extract dried over Na_2SO_4 . Solvent distilled off under reduced Pressure. Crude product purified by chromatography over silica gel. Yield : 2.5g.

% yield by theory: 25 - 30%

General procedure - VI - B

Example:

[0118]



O-acylation of m-phenoxyphenol

[0119] Hexanoyl chloride 7.70g (57.24 mmol) in 250 ml dry toluene was stirred with activated Zn dust 3.74g (57.24 mmol) at room temperature for 15 minutes, m-phenoxy phenol 4.5 g (24.2 M mole) in 150 ml toluene added and the reaction mixture stirred at 70 to 75°C for 30 minutes. Reaction mixture cooled to room temperature & filtered. Organic layer washed with 100 ml of 20% K_2CO_3 Solution followed by second washing with 15 ml of 20% K_2CO_3 Solution. Toluene layer washed with water, dried over Na_2SO_4 . Solvent distilled off under reduced pressure to get the product.

Yield: 6 g.

% yield by theory: 85%

Acylation also with carboxylic acid anhydrides

Fries rearrangement

[0120] O-hexanoate 0.8g (2.81 mmol) and AlCl_3 0.45g (3.47mmol) were mixed together in a round bottom flask. After 4 hr at 145-150°C, reaction mixture cooled to room temperature and worked up by pouring over 50ml 1:1 HCl (50ml) followed by extraction in DCM (100ml). Organic layer washed with water. Solvent evaporated off under reduced pressure. Crude reaction mass purified by silica gel column chromatography to get the pure product.

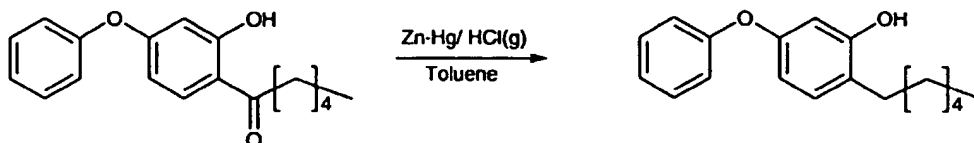
Yield : 0.6g

% yield by theory : 75%

General procedure - VII

Example:

[0121]

Reduction of keto to methylene by Clemmenson's method

[0122] Zinc amalgam was prepared from 12 g of Zn dust, 0.9g of mercury (II) chloride in 20 ml water and 2-3 ml HCl_{conc} . This was added to the solution of keto compd 1.5g (5.28 mmol) in 25 ml of toluene & 20ml HCl_{conc} . HCl gas bubbled into reaction mixture for 2 hr. 50 ml of toluene was added and toluene layer separated and washed with water. Solvent distilled off under reduced pressure to get the product.

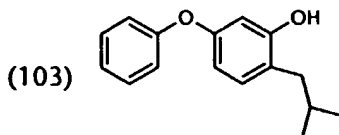
Yield : 1.45g

% yield by theory = 85-90%

Reduction also succeeds with H_2 , see Proc. III

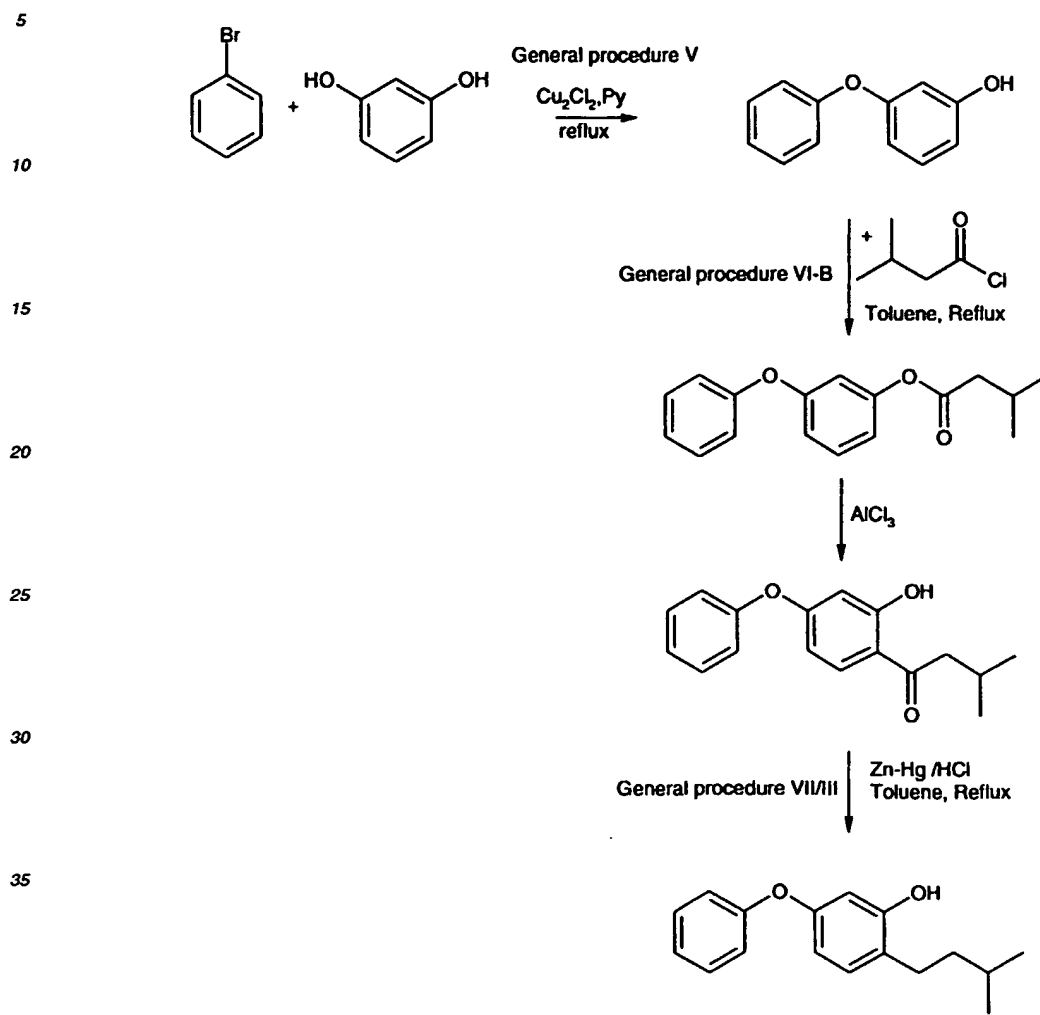
Example 5: Preparation of the compound of formula

[0123]

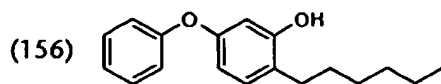


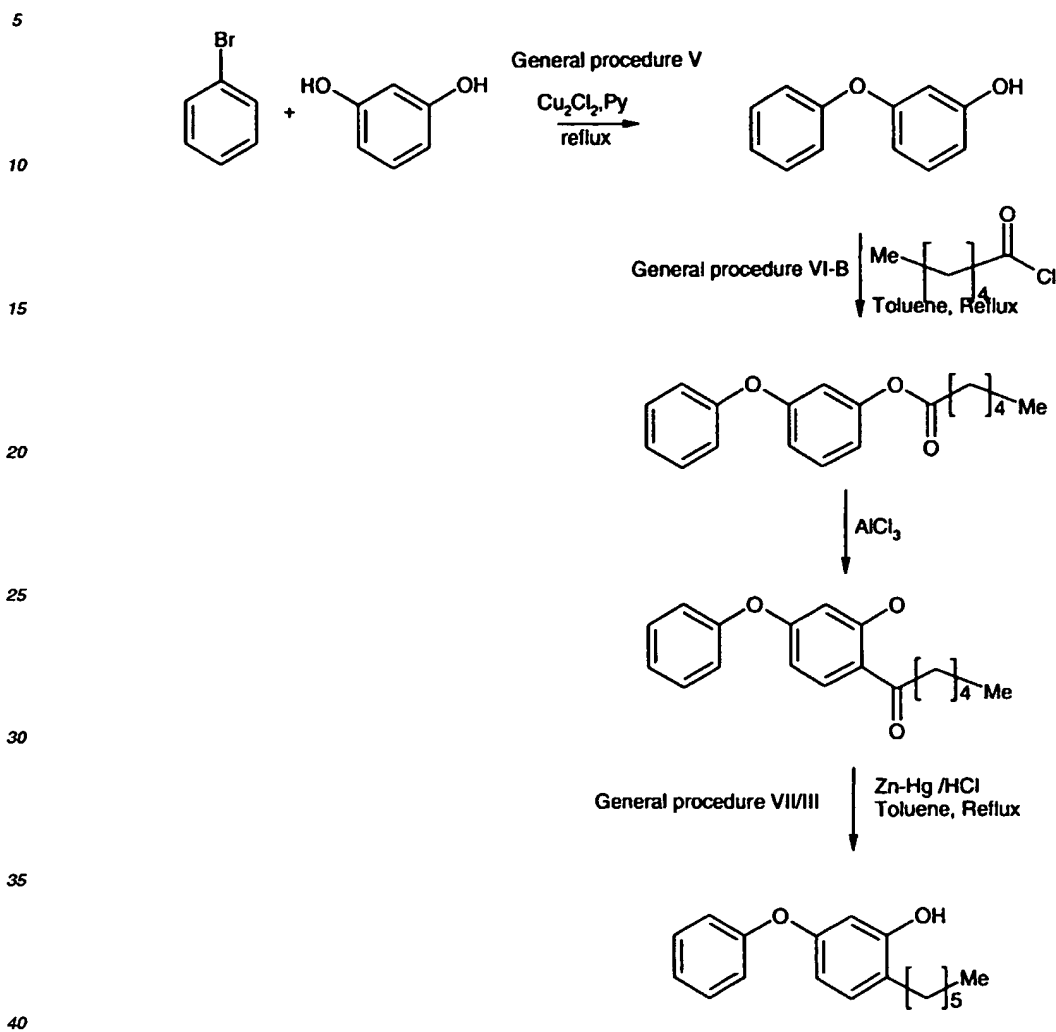
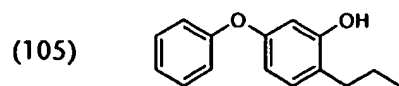
Reaction scheme:

[0124]

Example 6: Preparation of Compound of formula

[0125]



Reaction scheme:**[0126]**Example 7: Preparation of compound of formula**[0127]**

Reaction scheme:

[0128]

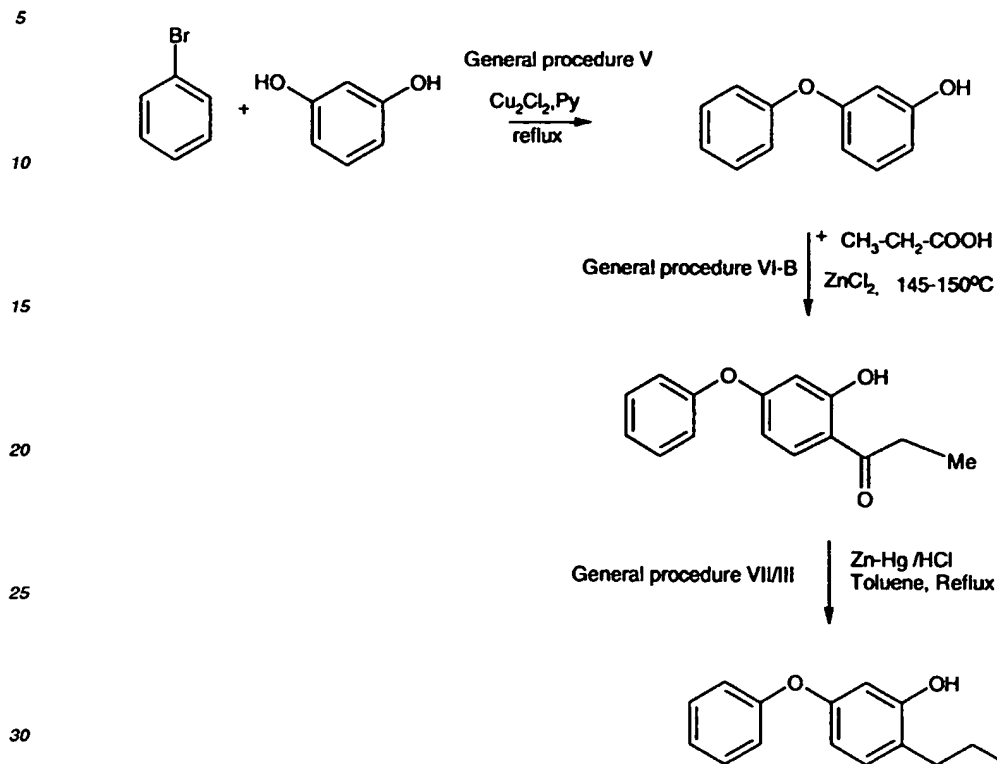


Table 3:

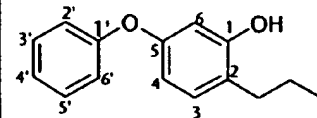
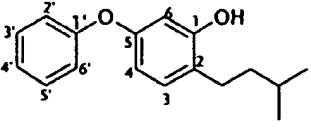
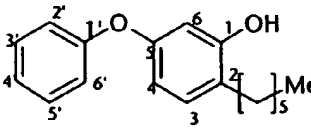
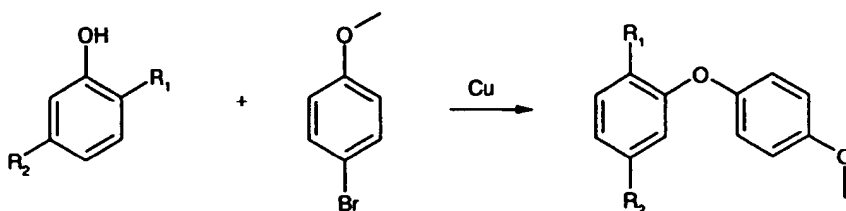
Compound	Reaction Protocols	m/e (M+1)	¹ H NMR (δ ppm)
 <p>(105)</p>	General procedure V, VIA / VIB & III / VII	229	0.9-1.0 (t, 3H, Me), 1.55-1.65 (m, 2H, -CH ₂ -), 2.4-2.5 (t, 2H, -CH ₂ -), 4.8 (s, 1H, -OH), 6.4-6.45 (d, 1H, H ^a Ar-H), 6.45-6.50 (dd, 1H, H ^a Ar-H), 6.95-7.05 (m, 4H, H ² , H ³ , H ⁵ , H ⁶ Ar-H),

Table 3:

Compound	Reaction Protocols	m/e (M+1)	1H NMR (δ ppm)
			7.25(d, 1H, H ³ Ar-H), 7.25-7.3(m, 1H, H ⁴ Ar-H)
 <p>(154)</p>	General procedure V, VIA / VIB & III / VII	257	0.9-1.0 (d, 6H, iso-pr), 1.4-1.55(m, 2H, >CH ₂ , >CH-), 2.6(t, 2H, -CH ₂ -), 4.8(s, 1H, -OH), 6.4 (d, 1H, H ⁶ Ar-H), 6.55-6.60(dd, 1H, H ⁴ Ar-H), 6.9-7.05(m, 4H, H ² , H ³ , H ⁵ , H ⁶ Ar-H), 7.25(d, 1H, H ³ Ar-H), 7.25-7.3(m, 1H, H ⁴ Ar-H)
 <p>(156)</p>	General procedure V, VIA / VIB & III / VII	271	0.9-1.0 (t, 3H, Me), 1.2-1.4(m, 6H, -CH ₂ -), 1.45-1.65(m, 2H, -CH ₂ -), 2.45-2.6(t, 2H, -CH ₂ -), 5.0(s, 1H, -OH), 6.4--6.5(d, 1H, H ⁶ Ar-H), 6.50-6.60(dd, 1H, H ⁴ Ar-H), 6.9-7.2(m, 4H, H ² , H ³ , H ⁵ , H ⁶ Ar-H), 7.3(d, 1H, H ³ Ar-H), 7.4(m, 1H, H ⁴ Ar-H)

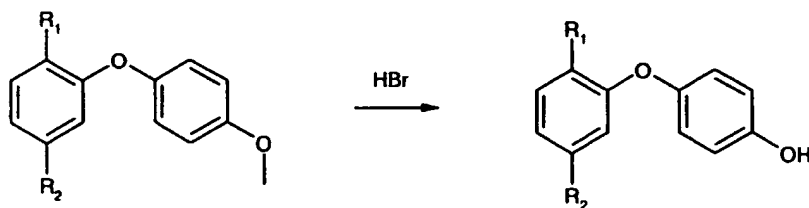
Example 8: Synthesis of 4-(2,5-Dialkylphenoxy)-phenols

[0129]



[0130] The mixture of 0.05 mol 2,5-Dialkylphenol, 2.8 g (0.05 mol) KOH, 0.4 g (0.006 mol) copper powder and 50 g (0.25 mol) bromo anisole is heated in a standard reaction apparatus, equipped with a water trap, to 160 °C for 5 h. After cooling the reaction mass is suspended in toluene and filtrated. After distilling off the solvent and excess reagent the product is isolated by distillation at 125 °C/0.01 mbar

R_1	R_2	Yield
Me	Me	4.6 g (40 %)
Me	i-Propyl	6.4 g (50 %)



[0131] 0.02 mol of the 4-(2,5-Dialkylphenoxy)-methoxybenzene and 30 ml HBr (47 % solution in water) are heated to reflux in 100 ml acetic acid for 4 h. After cooling and distilling off acetic acid the reaction mass is dissolved in 100 ml methylene chloride and washed with 200 ml water with pH adjusted to pH 10 with 10 % NaOH. Produkt is isolated from the organic phase by distillation at 160 °C/0.01 mbar, colourless oils.

R_1	R_2	Yield
Me	Me	2.2 g (52 %)
Me	i-Propyl	2.4 g (60 %)

Data $R_1 = R_2 = \text{Me}$:

[0132]

Elementary analysis:			
	$\underline{\text{C}}$	$\underline{\text{H}}$	$\underline{\text{O}}$
calc.	78.48	6.59	14.93
found	77.84	6.58	15.19

[0133] $^1\text{H-NMR}$ (CDCl_3): 2.15 (3H,s, CH_3), 2.20 (3H,s, CH_3), 4.65 (1 H,s,OH), 6.55 - 7.05 (7H,m,arom. H)

Mass spectrum: m/z [M^+] = 214

Data $R_1 = \text{Me}$, $R_2 = i\text{-Propyl}$:

[0134]

Elementary analysis:			
	<u>C</u>	<u>H</u>	<u>O</u>
calc.	79.30	7.49	13.21
found	77.82	7.30	13.61

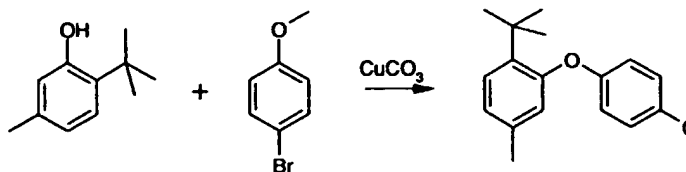
[0135] $^1\text{H-NMR}$ (CDCl_3): 1.05 (3H,s, CH_3), 1.08 (3H,s, CH_3), 2.10 (3H,s, CH_3), 2.70 (1 H,s,CH), 4.85 (1H,s,OH), 6.60 - 7.05 (7H,m,arom. H)

Mass spectrum: m/z [M^+] = 242

Example 9: Synthesis of 4-(2-t-Butyl-5-methylphenoxy)phenol

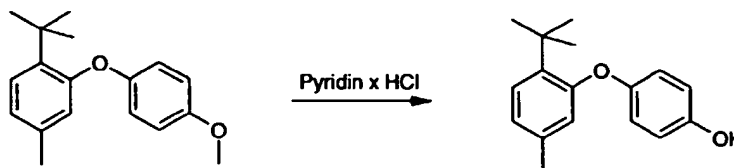
Reaction scheme:

[0136]



[0137] The mixture of 16.4 g (0.1 mol) 2-t-butyl-5-methylphenol and 1.8 g (0.03 mol) KOH in 100 ml xylene is heated in a standard reaction apparatus, equipped with a water trap, to reflux until no more water is distilling. After addition of 0.2 g basic copper carbonate and 18.7 g (0.1 mol) bromo anisole the mixture is heated to reflux for 20 h. After cooling the reaction mass is filtrated and solvent and excess reagents are distilled off. The product is isolated by distillation at 100 °C/0.01 mbar.

Yield: 7.1 g (81 %).



[0138] 7.1 g (0.026 mol) of 4-(2-t-Butyl-5-methylphenoxy)-methoxybenzene are heated with 15.0 g (0.13 mol) pyridinium hydrochloride to 180°C for 6 h. After cooling water is added and the reaction mass is extracted with xylene. The product is distilled after evaporation of xylene at 130°C / 0.01 Torr and recrystallized from petrol ether (80 - 110) to yield colourless crystals (mp 102°C).

Yield: 4.6 g (69 %)

Elementary analysis:			
	<u>C</u>	<u>H</u>	<u>O</u>
calc.	79.65	7.86	12.48
found	78.96	7.55	11.59

[0139] ¹H-NMR (CDCl₃): 1.41 (9H,s,C(CH₃)₃), 2.21 (3H,s,CH₃), 4.75 (1 H,s,OH), 6.58 - 7.25 (7H,m,arom. H)
Mass spectrum: m/z [M⁺] = 256

Microbiological data of the above compounds (MIC in ppm):

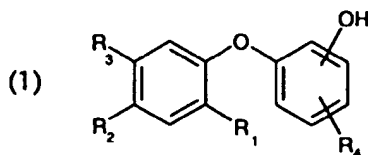
[0140]

Table 4:

Microorganisms	Substance		
	R ₁ = t-Butyl R ₂ = Me	R ₁ = Me R ₂ = i-Propyl	R ₁ = R ₂ = Me
Staphylococcus aureus ATCC 6538	6.75ppm	6.25ppm	50.0ppm
Staphylococcus epidermidis ATCC 12228	3.4ppm	6.25ppm	25.0ppm
Corynebacterium xerosis ATCC 373/ATCC 7711	3.4ppm	3.125ppm	25.0ppm
Staphylococcus hominis DSM 20328		6.25ppm	--
Corynebacterium minutissimum ATCC 23348	3.4ppm	6.25ppm	25.0ppm
Propionibacterium acnes ATCC 11829	5ppm	10ppm	--
Escherichia coli NCTC 8196	>100ppm	>200ppm	>200ppm
Proteus vulgaris ATCC 6896	>100ppm	>200ppm	>200ppm
Pseudomonas aeruginosa CIP A-22	>100ppm	>200ppm	>200ppm
Candida albicans ATCC 10231	12.5ppm	12.5ppm	25.0ppm
Aspergillus niger ATCC 6275	6.75ppm	50ppm	--
Epidermophyton floccosum CBS 55384	1.65ppm	<3.125ppm	--
Trichophyton mentagrophytes ATCC 9553	3.4ppm	6.25ppm	--
Trichophyton rubrum DSM 4167	10ppm	5ppm	--
Malassezia furfur DSM 6171	2.5ppm	--	--
Actinomyces viscosum DSM 43329	5ppm	80ppm	--
Porphyromonas gingivalis DSM 20709	1.25ppm	5ppm	--
Selenomonas artemidis ATCC 43528	5ppm	10ppm	--
Streptococcus sobrinus DSM 20742	5ppm	5ppm	--

Claims

1. Use of hydroxydiphenyl ether compounds of the following formula



wherein when OH is in the para position with respect to the ether linkage

R_1 and R_2 are independently of each other hydrogen, hydroxy, C_1 - C_{20} alkyl, C_5 - C_7 cycloalkyl, C_1 - C_6 alkylcarbonyl, C_1 - C_{20} alkoxy, phenyl or phenyl- C_1 - C_3 -alkyl;

R_3 is hydrogen, C_1 - C_{20} alkyl or C_1 - C_{20} alkoxy;

R_4 is hydrogen, C_1 - C_{20} alkyl, hydroxy substituted C_1 - C_{20} alkyl, C_5 - C_7 cycloalkyl, hydroxy, formyl, acetylonyl, C_1 - C_6 alkylcarbonyl, C_2 - C_{20} alkenyl, carboxy, carboxy- C_1 - C_3 alkyl, C_1 - C_3 alkylcarbonyl- C_1 - C_3 alkyl or carboxyallyl;

wherein when OH is in the meta position with respect to the ether linkage

R_2 is hydrogen, C_1 - C_{20} alkyl, hydroxy substituted C_1 - C_{20} alkyl or C_1 - C_6 alkylcarbonyl;

R_1 and R_3 are independently of each other hydrogen, C_1 - C_6 alkylcarbonyl or C_1 - C_{20} alkyl;

R_4 is hydrogen, C_1 - C_{20} alkyl, hydroxy substituted C_1 - C_{20} alkyl, C_5 - C_7 cycloalkyl, hydroxy, formyl, acetylonyl, C_1 - C_6 alkylcarbonyl, C_2 - C_{20} alkenyl, carboxy, carboxy- C_1 - C_3 alkyl, C_1 - C_3 alkylcarbonyl- C_1 - C_3 alkyl or carboxyallyl;

wherein when OH is in the ortho position with respect to the ether linkage

R_1 is hydrogen, C_1 - C_6 alkyl carbonyl or C_1 - C_{20} alkyl;

R_4 is hydrogen, C_1 - C_{20} alkyl, hydroxy substituted C_1 - C_{20} alkyl, C_5 - C_7 cycloalkyl, hydroxy, formyl, acetylonyl, C_1 - C_6 alkylcarbonyl, C_2 - C_{20} alkenyl, carboxy, carboxy- C_1 - C_3 alkyl, C_1 - C_3 alkylcarbonyl- C_1 - C_3 alkyl or carboxyallyl;

R_2 and R_3 are independently of each other hydrogen, C_1 - C_6 alkyl carbonyl or C_1 - C_{20} alkyl;

with the proviso that compounds wherein OH is in the para position with respect to the ether linkage and R_1 and R_3 are both hydrogen and R_2 is methoxy or methyl; or a compound wherein OH is in the para position with respect to the ether linkage R_2 is hydrogen, R_1 is isopropyl and R_3 is methyl are excluded; as antimicrobial agents.

2. Use of the compounds according to claim 1 wherein in formula (1) when OH is in the para position with respect to the ether linkage

R_1 and R_2 are independently of each other hydrogen, C_1 - C_{20} alkyl, C_1 - C_6 alkyl carbonyl or C_1 - C_{20} alkoxy;

R_3 is hydrogen, C_1 - C_{20} alkyl or C_1 - C_{20} alkoxy;

R_4 is hydrogen, C_1 - C_{20} alkyl, hydroxy, formyl, acetylonyl, allyl, carboxymethyl, carboxyallyl, hydroxy substituted C_1 - C_{20} alkyl or C_1 - C_6 alkyl carbonyl;

wherein when OH is in the meta position with respect to the ether linkage

R_2 is hydrogen, C_1 - C_{20} alkyl, hydroxy substituted C_1 - C_{20} alkyl or C_1 - C_6 alkyl carbonyl;

R_1 and R_3 are independently of each other hydrogen, C_1 - C_6 alkyl carbonyl or C_1 - C_{20} alkyl;

R_4 is hydrogen, C_1 - C_{20} alkyl, hydroxy, formyl, acetylonyl, allyl, carboxymethyl, carboxyallyl, hydroxy substituted C_1 - C_{20} alkyl or C_1 - C_6 alkyl carbonyl;

wherein when OH is in the ortho position with respect to the ether linkage

R_1 is hydrogen, C_1 - C_6 alkyl carbonyl or C_1 - C_{20} alkyl;

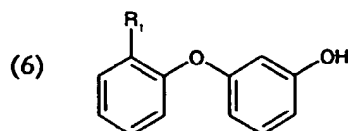
R_4 is hydrogen, C_1 - C_{20} alkyl, hydroxy, formyl, acetylonyl, allyl, carboxymethyl, carboxyallyl, hydroxy substituted C_1 - C_{20} alkyl or C_1 - C_6 alkyl carbonyl;

R_2 and R_3 are independently of each other hydrogen, C_1 - C_6 alkyl carbonyl or C_1 - C_{20} alkyl;

with the proviso that compounds wherein OH is in the para position with respect to the ether linkage and R_1 and

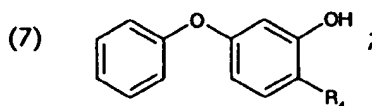
R₃ are both hydrogen and R₂ is methoxy or methyl; or a compound wherein OH is in the para position with respect to the ether linkage R₂ is hydrogen, R₁ is isopropyl and R₃ is methyl are excluded.

3. Use of the compounds of formula



according to claim 1, wherein
R₁ is C₁-C₅alkyl.

4. Use of the compounds of formula



wherein
R₄ is C₁-C₅alkyl.

5. Use of the compounds according to one of claims 1 to 4 for finishing of undyed and dyed or printed fibre materials.

6. Use of the compounds according to one of claims 1 to 4 for the antimicrobial treatment of skin, mucous membrane or hair.

7. Use of the compounds according to one of claims 1 to 4 for the incorporation into and for the antimicrobial finishing of polymeric materials.

8. Use of the compounds according to one of claims 1 to 4 for the antimicrobial treatment of hard surfaces.

9. Use of the compounds according to one of claims 1 to 4 for the antimicrobial treatment of teeth and gums.

10. A personal care composition comprising at least one compound of formula (1) according to claim 1 and cosmetically tolerable carriers or auxiliaries.

11. An oral care composition comprising at least one compound of formula (1) according to claim 1.

12. A detergent composition comprising at least one compound of formula (1) according to claim 1.

13. Compounds of formula (1) wherein OH is in the ortho position with respect to the ether linkage and R₂, R₃ and R₄ are hydrogen and R₁ is C₁-C₂₀ alkyl.

14. Compounds of formula (1) wherein OH is in the meta position with respect to the ether linkage and R₂, R₃ and R₄ are hydrogen and R₁ is C₁-C₂₀ alkyl.

15. Compounds of formula (1) wherein OH is in the para position with respect to the ether linkage and R₂ and R₄ are hydrogen and R₁ and R₃ are C₁-C₂₀ alkyl.

16. A process for the preparation of compounds according to one of claims 13 to 15 comprising reacting a substituted phenol with an ether substituted halogenphenol in the presence of alkali and a catalytically active quantity of copper or of a copper compound, then heating the resulting alkyloxybenzol compound in the presence of hydrogen halide

and acid.

17. Compounds of formula (1) wherein OH is in the ortho position with respect to the ether linkage and R₁, R₂ and R₃ are hydrogen and R₄ is in the meta position with respect to the ether linkage and is C₁-C₆ alkyl carbonyl.

18. Compounds of formula (1) wherein OH is in the meta position with respect to the ether linkage and R₁, R₂ and R₃ are hydrogen and R₄ is in the para position with respect to the ether linkage and is C₁-C₆alkyl carbonyl.

19. A process for the preparation of compounds according to claims 17 and 18 which comprises reacting an acyl chloride with a phenoxyphenol in the presence of activated zinc at a temperature of between 70°C to 80°C, then heating the resulting acyl compound at a temperature of 145°C to 150°C in the presence of aluminium chloride.

20. Compounds of formula (1) wherein OH is in the meta position with respect to the ether linkage and R₁, R₂ and R₃ are hydrogen and R₄ is in the para position with respect to the ether linkage and is C₁-C₂₀alkyl.

21. A process for the preparation of compounds according to claims 17 and 18 which comprises reacting an acyl chloride with a phenoxyphenol in the presence of activated zinc at a temperature of between 70°C to 80°C, then heating the resulting acyl compound at a temperature of 145°C to 150°C in the presence of aluminium chloride, then refluxing the resulting acylated phenol in the presence of amalgamated zinc, hydrochloric acid and a solvent such as toluene.